Award Number: W81XWH-11-1-0826

TITLE: Home-Based Diagnosis and Management of Sleep-Related Breathing Disorders in Spinal Cord Injury

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REPORT DATE: February 2016

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

*Form Approved
OMB No. 0704-0188*

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. **PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
February 2016	Final	30 Sep 2011 - 1 Feb 2016

4. TITLE AND SUBTITLE

Home-Based Diagnosis and Management of Sleep-Related Breathing Disorders in Spinal Cord Injury

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-11-1-0826

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT Patients with spinal cord injury (SCI) commonly have sleep-disordered breathing (SDB) due to obstructive sleep apnea (OSA) and/or nocturnal hypoventilation (NH). In the general population, OSA has been linked to cardiovascular morbidity, glucose intolerance, obesity, and hyperlipidemia, all common co-morbidities with SCI. The impact of SDB in SCI has received little attention. Conventionally, SDB is diagnosed by a facility-based polysomnogram (PSG), which is often unavailable to SCI patients because of logistical obstacles. Our hypothesis is that unrecognized SDB is common, can be diagnosed by home-based testing, and contributes to the morbidity of patients with SCI. This project is a prospective cohort study targeting 100 subjects with C1-T6 SCI. SDB is assessed in subjects' homes with a limited PSG combined with overnight oxygen saturation (SpO2)/transcutaneous pCO_2 (tc-pCO_2) monitoring. OSA and NH are treated with noninvasive ventilatory support according to usual standards of care. Subjects are being followed prospectively for 1 year with periodic laboratory studies, quality of life surveys, and daily symptom/event logs. The specific aims are: 1A: Determine the prevalence of OSA and NH in SCI patients. 1B. Establish the feasibility of home-based PSG's with SpO_2/tc-pCO_2 monitoring in SCI patients. 2A: Determine whether there are reliable clinical predictors for OSA or NH, and for compliance with noninvasive ventilation. Determine the impact of early recognition and treatment of OSA and NH on: 3A. quality of life, 3B. pulmonary morbidity, 3C. blood pressure instability, and 3D. features of the "metabolic syndrome" (obesity, diabetes, hyperlipidemia). At the completion of year 4, we have 1. completed enrollment at 93 subjects, 2. 81 subjects completed both their home sleep study and SpO_2-tc-pCO_2 monitoring. Of these, 82.1% had OSA, 23.8% had central sleep apnea, and 28% had NH. OSA correlated only with neck circumference, while central sleep apnea correlated with use of sedatives and OSA. There were no reliable predictors for NH. Treatment of SDB with noninvasive ventilatory support may reduce autonomic dysreflexia and orthostatic dizziness) and some aspects of quality of life. There were no discernible effects of noninvasive ventilatory support on laboratory indices of glucose intolerance or dyslipidemia. Adherence to treatment is difficult to predict, often suboptimal, and highly variable.

15. SUBJECT TERMS
Spinal cord injury, sleep-related breathing disorder, sleep apnea, hypoventilation

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
U	U	U	UU	49	

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FINAL PROGRESS REPORT

INTRODUCTION Patients with spinal cord injury (SCI) commonly have sleep-disordered breathing (SDB), often caused by closure of the upper airway (obstructive sleep apnea; OSA). Other forms of SDB breathing in SCI include central sleep apnea (CSA) and central hypoventilation due to respiratory muscle paralysis and/or reduced ventilatory drive during sleep. If sufficiently severe, any form of SDB can cause decreased blood levels of oxygen (pO_2) and/or nocturnal hypercapnia (NH), which refers to increased blood levels of carbon dioxide (pCO_2). In the general population, OSA is associated with increased risk for myocardial infarction, stroke, congestive heart failure, and the "metabolic syndrome" (increased visceral fat, hypertension, glucose intolerance, and hyperlipidemia). We know very little about the adverse clinical consequences of OSA or NH in SCI. Increased cardiovascular morbidity, diabetes and obesity are all common in SCI, supporting the hypothesis underlying this proposal: Unrecognized SDB is common in SCI, adversely affects quality of life (QoL), and contributes to many of the co-morbidities associated with SCI.

Standard sleep studies (polysomnograms; PSG) monitor airflow, chest movement, and oxygen desaturation to detect interruptions in breathing, but pCO_2 measurements are not done routinely, so nocturnal hypoventilation with CO_2 retention may go undetected. Data on SDB in SCI has been collected largely from studies performed in sleep laboratories. Unfortunately, PSG are often not done at all in SCI because patients refuse or are denied reasonable access to sleep laboratories (wheelchair-accessibility and facilities for SCI care, accommodations for caregivers). Therefore, it is likely that clinically significant SDB often goes unrecognized in SCI patients. Recent technological advances enabled us to collect valid data from home-based studies for both OSA and NH. The potential advantages of home-based testing include improved convenience/acceptance by patients and families, increased diagnostic yield, and reduced cost. Our hypothesis was that SDB can be diagnosed reliably and efficiently in SCI patients by home-based testing.

This project was a prospective cohort study targeting 100 subjects with C1-T6 SCI. SDB was assessed in subjects' homes with a limited PSG combined with overnight oxygen saturation (SpO_2)/transcutaneous pCO_2 (tc-pCO_2) monitoring. OSA and NH were treated bi-level positive pressure ventilation (PPV) according to usual standards of care. Subjects were followed prospectively for 1 year with periodic laboratory studies, quality of life surveys, and daily symptom/event logs. Once SDB was identified, current standards of care were applied to determine treatment with noninvasive ventilatory support. The specific aims were:

Aim 1: A. Determine the prevalence of OSA and NH in ventilator-independent SCI patients. B. Establish the feasibility of unsupervised home-based PSG with overnight SpO_2/tc-pCO_2 monitoring to diagnose SDB in SCI patients.

Aim 2: Determine whether there are reliable clinical predictors for A. the presence of OSA or NH, and B. compliance with noninvasive ventilatory support.

Aim 3: Determine how early recognition and treatment of SDB affects A. quality of life, B. pulmonary morbidity, C. autonomic dysfunction (blood pressure instability), and D. features of the metabolic syndrome (obesity, diabetes, hyperlipidemia).

BODY

Recruitment (SOW tasks 1-8):
Subject recruitment began on March 2, 2012, and was completed in July 2014. 93 subjects were recruited, provided informed consent, and commenced the study protocol. One hundred fifty nine (159) other potential subjects were contacted, and were either ineligible or refused to enroll. We suspended recruitment in July 2014 because we had approached all subjects in our approved recruiting base (subjects enrolled in the University of Michigan Spinal Cord Injury Model Program living within ~100 miles of Ann Arbor MI). We terminated further recruitment at that time because any new entries into the recruitment

base could not complete the study protocol before the study end date in 2015. This brought us very close to reaching the target enrollment of 100 subjects.

Study Protocol (SOW tasks 1-8)
After consent was obtained, the first phase of the study protocol was a 4 month period where subjects kept daily symptom/event logs. These data provided the pre-diagnosis/treatment baseline for SOW tasks 6 and 7. The table below indicates the numbers of subjects that either withdrew from the study or were excluded from the study protocol at each time point. Subjects that withdrew from the study generally did so because they were unwilling to continue with the time commitment, or lost interest when they saw that they were noncompliant with bi-level PPV.

FIGURE 1: FLOW DIAGRAM OF STUDY PROTOCOL, INCLUDING RECRUITMENT AND ATTRITION
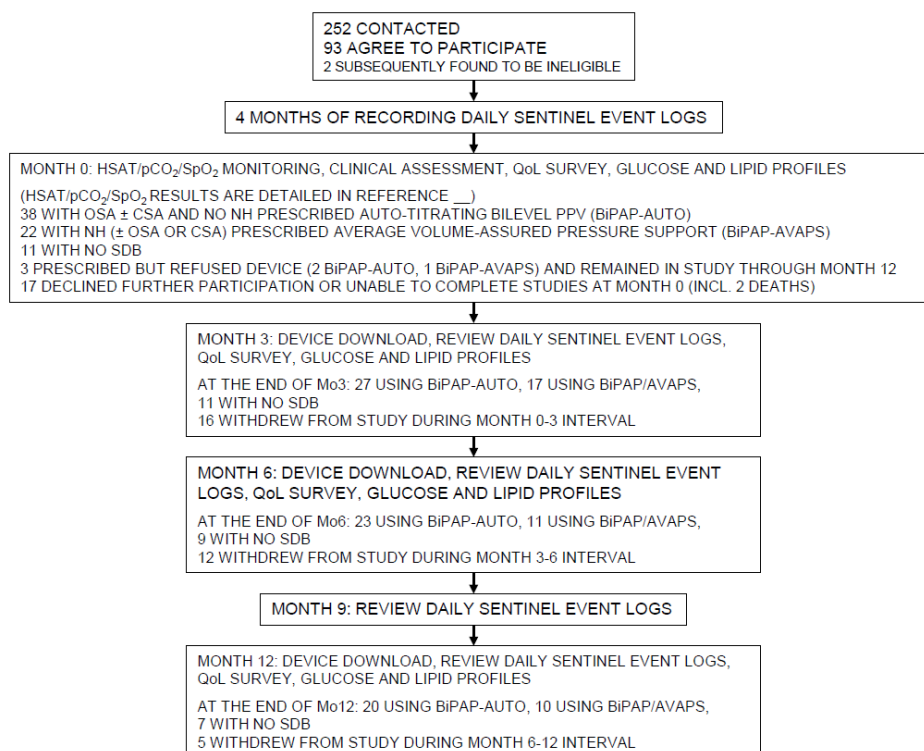
Adverse events, incidents, protocol violations
There were no adverse events or subject complaints related to any phase of the study. There were two deaths due to unrelated complications of SCI. There were no major violations of protocol (missed studies, omissions in completing questionnaires or testing). Compliance with symptom/event logs was very good.

Summary of Findings for Specific Aims 1 and 2A. In the year 3 and 4 progress reports, we reported many of the findings related to Specific Aims 1 and 2A; since then, our findings were reported in final form and accepted for publication.
These findings are presented in detail in APPENDIX 3; Bauman KA, Kurili A, Schotland HM, Rodriguez GM, Chiodo AE, Sitrin RG, A Simplified Approach to Diagnosing Sleep Disordered Breathing and Nocturnal Hypercapnia in Individuals with Spinal Cord Injury, *ARCHIVES OF PHYSICAL MEDICINE AND REHABILITATION* (2015), doi: 10.1016/j.apmr.2015.07.026.)

- 91 eligible subjects agreed to participate in the study. After 4 months' observation to establish clinical stability, home sleep apnea tests (HSAT), and tc-pCO$_2$/SpO$_2$ studies were performed. Seventy-five male and 16 female subjects, age 47.7 ± 12.3 years (mean ± SD, range 20-75 years) enrolled. Subjects were 16.8 ± 12.0 years post-injury (mean ± SD, range 1-50 years). Sedating medications prescribed at the time of the home sleep apnea test (HSAT) included baclofen in 78%, benzodiazepines in 43%, and ≥ 1 others (most commonly, analgesics) in 71%. 31% were prescribed medications in two classes, and 38% were prescribed medications in all three. Ten patients did not complete this phase of the study.
- Obstructive sleep apnea was detected in 81.3% of subjects, with a wide range of severity. Neck circumference is the strongest predictor; however, this positive association only explained 17% of the variation in the obstructive apnea/hypopnea index (O-AHI). After accounting for neck circumference, no other predictor was even weakly associated with the O-AHI.
- Events of reduced breathing that could not be characterized were scored as nonspecific hypopnea events (NSHE). In the majority, there were few such events, but in 35%, there were ≥ 5 events /hr,, including ≥ 10 events/hr in 20%,. There was a very tight correlation between central sleep apnea (CSA) and NSHE events. The correlation between NSHE and O-AHI, although statistically significant, was much lower; suggesting that most NSHE events are central hypopneas. Our data suggests that our more stringent definition of OSA prevented mis-classification of central events as obstructive, and accordingly there was no over-estimation of OSA.
- Central sleep apnea was found in 23.8% and 10% had ≥ 15 central apnea events/hr. Sedating medications and log O-AHI correlated with CSA. In multiple regression analysis, only sedating drug use and O-AHI were predictive of CSA. Unlike OSA, measurements of body shape had no association with CSA. Surprisingly, the frequency of CSA events did not correlate with the motor level of SCI.
- Nocturnal hypercapnia (NH) was detected in 28%, for a median of 25% of the study time, (IQR 11-72%; maximum 100%). The median peak tc-pCO$_2$ was 56.7 mmHg (IQR 53.9-61mmHg; maximum 95mmHg). Awake tc-pCO$_2$ was the only clinical feature with significant predictive value for NH.
- Nocturnal oxygen desaturation was seen in 15 (18.3%) subjects, only 5 of whom had NH. This generally occurred in subjects with mild/moderate OSA (median O-AHI 19.7), and little or no CSA (median CSA 0.3 events/hr). Therefore, oxygen desaturation cannot serve as a surrogate for tc-pCO$_2$ measurement, and does not reflect the severity of either OSA or CSA.

Adherence with Therapy (Specific Aim 2B)

- Adherence (compliance) with noninvasive ventilatory support was determined from data downloaded directly from the bi-level PPV device prescribed to the patients, rather than relying on patient/caregiver surveys.
- Summarizing the data collected over the first 3 months of use (Mo 3), we found that adherence with bi-level PPV was highly variable. The median minutes of use/night on the days the device was used at all was 185 min/night, IQR 56.5-312 min/night A few patients improved and others decreased their adherence over time, but overall we saw no change in use at months 6 or 12 (not shown).
- The other main adherence parameter we examined was the % of days that the device was used at all. At Mo3, the median % of days was 33%, IQR 8.5-85%. After 3 months of treatment, only 39% used their device for ≥ 50% of nights. Again, there was no overall change in use at months 6 or 12.
- To assess the effectiveness of BiPAP-auto and BiPAP/AVAPS, the device downloads were reviewed according the study protocol (Table 1). The primary data analysis was performed for the Month 0-3 interval. 40.7% had a residual AHI >5 events/hr, but these subjects mostly had residual hypopneas, and by protocol, these patients were assigned BiPAP-auto because these hypopneas were not associated with hypercapnia. BiPAP-auto completely corrected obstructive apneas (residual obstructive apneas ≤ 5

events/hr) in 88.9%. There were only 14.8% on BiPAP-auto that had significant central apneas (≥ 5 central events/hr and $\geq 50\%$ of all events). Central events decreased by 20.7 and 0.1 events/hr in 2 subjects, and increased by only 2.4 and 2.6 events/hr in 2 others. At Mo3, BiPAP/AVAPS treatment resulted in complete control of nocturnal hypercapnia in 82.4%; in the remainder, the residual hypercapnia was very mild (Appendix 4).

- To determine whether we could find any predictors for device adherence (specific aim 2B), we sought to determine if there were significant predictors among key clinical variables or device settings. Using linear regression models, we found that over the first 3 months of PPV use, the minutes used per night (on days of use) could not be predicted at all by the SCI motor level, the overall severity of SDB (sum of obstructive and central apneas, and hypopnea events), the type of mask interface (nasal or nasal pillows vs. full- or total face mask), or device type (BiPAP-auto or BiPAP/AVAPS). These results are detailed in our manuscript, currently in submission (Appendix 4).

- We found that over the Mo0-3 interval, the average expiratory pressure EPAP: cmH_2O) had significant predictive value for both the minutes used per night and % of nights used for subjects using BiPAP-auto. Given that there was no correlation between use and apnea severity (O-AHI), this suggests to us that a higher EPAP may either be more comfortable for the subject, or the higher pressure suggests to the subject that the treatment is more effective, as opposed to lower pressures which may be difficult to perceive. Similarly, over the same Mo0-3 interval, the average inspiratory pressure (IPAP) had significant predictive value for both the minutes used per night and % of nights used for subjects using BiPAP/AVAPS, and in this case it was the EPAP (a fixed setting not affected by the titration algorithm) that had no predictive value. Thus, for both types of BiPAP devices, it seems that the device settings that figure prominently in the auto-titration algorithm are important factors in motivating the patient to use their device. These results are detailed in our manuscript, currently in submission (Appendix 4).

- Having reviewed these data, we suspect that in future studies, %-of-days-used is a parameter of adherence that may require a somewhat different treatment than minutes-used-per-night on days of use. Many subjects reported that they would discontinue bi-level PPV treatment for significant periods when they had unrelated illnesses such as urinary tract infections or decubitus ulcers. They often expressed the opinion that PPV was only acceptable when there were no active, major comorbidities. By contrast, they often related that minutes of use-per-night was more a function of overall sleep quality (a chronic problem for many SCI patients), comfort, or perceived benefit. While many important questions remain, these findings show that a. adherence with bi-level PPV is highly variable and often suboptimal, b. the frequency of use and duration of use per night may best be analyzed in subsequent studies by detailed survey information collected daily and targeted to ascertain what determined the level of use for the previous night. Data collected over the long-term, such as device downloads and periodic surveys, while helpful in some respects, may not suffice to understand the major determinants of adherence to treatment.

Quality of Life Surveys (Specific Aim 3A)

At the same intervals as logging sentinel events, subjects completed quality of life surveys, including the SF-12, brief pain survey, and Epworth sleepiness scores. On an intention-to treat basis, we found significant improvement in responses to any of the survey instruments over the study period, as follows:

Table 1: Quality of Life Survey Summary

INTENT-TO-TREAT COHORT[1]

	Month 0	Month 3	Month 6	Month 12

1: In general, would you say your health is:
1: poor 2: fair 3 good 4: very good 5 excellent

Month 0	Month 3	Month 6	Month 12
3.3	NS	NS	3.6 (p=0.048)

3: During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?
A: Accomplished less than you would like
1: all of the time 2: most of the time, 3: some of the time 4: a little of the time 5: none of the time

Month 0	Month 3	Month 6	Month 12
2.9	NS	NS	3.5 (p=0.01)

5: During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?
1. not at all 2. a little bit 3: moderately 4: quite a bit 5 extremely

Month 0	Month 3	Month 6	Month 12
2.8	2.4 (p=0.004)	2.4 (p=0.004)	NS

6: These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>.
C. Have you felt downhearted and depressed?
1: all the time 2: most of the time 3: some of the time 4: a little of the time 5: none of the time

Month 0	Month 3	Month 6	Month 12
3.8	NS	NS	4.0 (p=0.03)

Epworth Sleepiness Scale (total points)

Month 0	Month 3	Month 6	Month 12
8.3	NS	NS	6.8 (p=0.007)

SUBJECTS WITHOUT SLEEP-DISORDERED BREATHING[1]

13: On a scale from 0 to 10, with 0 being No Pain and 10 being Pain as Bad as You Can Imagine, please rank how much pain you have right now

Month 0	Month 3	Month 6	Month 12
3.9	3.0 (p=0.045)	NS	NS

Epworth Sleepiness Scale (total points)

Month 0	Month 3	Month 6	Month 12
9.4	5.9 (p=0.007)	NS	NS

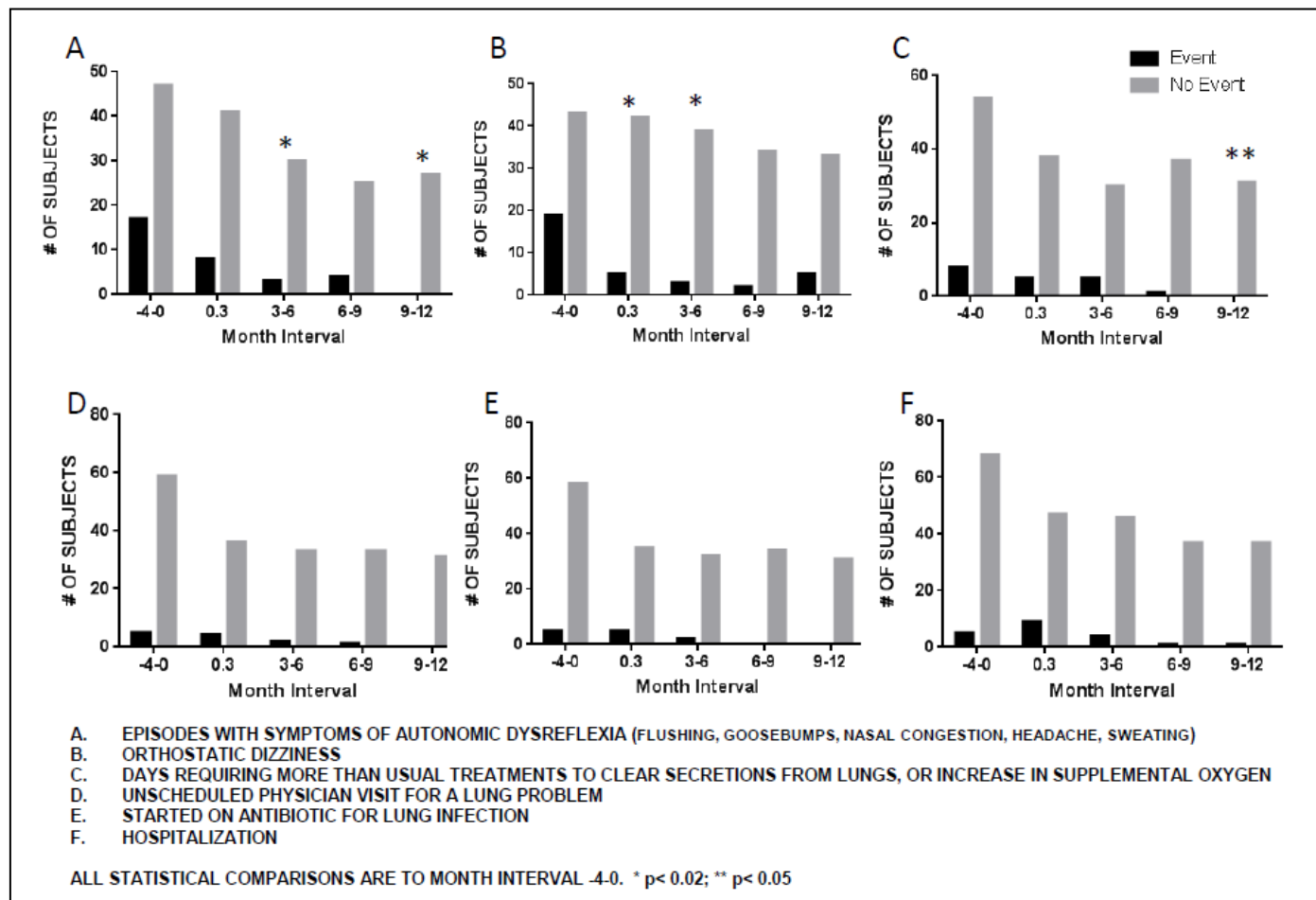[1]ONLY QUESTIONS WITH SIGNIFICANT CHANGES FROM MONTH 0 AT ≥ TIME POINT ARE LISTED

These findings indicate that there were several significant improvements in quality of life over the study period. Given the erratic adherence to treatment and variations in co-morbidities, perhaps it is not surprising that these improvements were not maintained consistently for the 12 months of follow-up. By contrast, the small cohort of subjects without SDB showed only a transient improvement in the pain score (question 13). The Epworth sleepiness scale did also improve transiently, as it did in the intent-to-treat group. The significance of this finding is questionable, as we saw in our initial analysis of this group that the Epworth score was a particularly poor predictor of SDB (Appendix 4).

Event Logs (Specific Aims 3A-C)
During the initial run-in period prior to the home sleep studies, and for the following year, subjects collected data in daily logs to determine the frequency of certain events, based on our hypothesis that these events may be impacted by treatment of SDB and/or nocturnal hypercapnia. On an intention-to-treat basis, the data show at several time points highly significant reductions in the frequency of blood pressure instability, both autonomic dysreflexia reactions (episodes with symptoms including flushing, piloerection, nasal congestion, headache, or sweating), and orthostatic hypotension (lightheadedness or dizziness when sitting up or changing position), p<0.001 for both. In addition, the frequencies of days with pulmonary symptoms (requiring more than usual treatments to clear secretions, or an increase in oxygen use)

decreased at Month 12 compared to Month 0. There were no significant reductions in less frequent events, including the frequency of unscheduled physician visits for lung problems, antibiotic prescriptions for lung infections, or hospitalizations. These finding suggest that these reductions in important events are major short-term benefits of treating SDB. Unfortunately, we still have to consider this an unproven hypothesis worthy of further study, as we only had 11 subjects who had neither SDB or nocturnal hypercapnia, and almost none of these patients ever had any of these sentinel events at or before Time 0. For this reason, we cannot conclude that the reductions in reported sentinel events are definitely related to treatment, and not an unintended by-product of study participation.

FIGURE 2: EFFECTS OF TREATMENT ON SENTINAL EVENTS

A. EPISODES WITH SYMPTOMS OF AUTONOMIC DYSREFLEXIA (FLUSHING, GOOSEBUMPS, NASAL CONGESTION, HEADACHE, SWEATING)
B. ORTHOSTATIC DIZZINESS
C. DAYS REQUIRING MORE THAN USUAL TREATMENTS TO CLEAR SECRETIONS FROM LUNGS, OR INCREASE IN SUPPLEMENTAL OXYGEN
D. UNSCHEDULED PHYSICIAN VISIT FOR A LUNG PROBLEM
E. STARTED ON ANTIBIOTIC FOR LUNG INFECTION
F. HOSPITALIZATION

ALL STATISTICAL COMPARISONS ARE TO MONTH INTERVAL -4-0. * $p < 0.02$; ** $p < 0.05$

Metabolic Syndrome (Specific Aim 3D)

- At initial evaluation, 7 of 77 subjects (9.1%) had previously been diagnosed with diabetes mellitus (DM). An additional 3 met the diagnostic criteria for DM based on an elevated 2 hour post-prandial glucose level, and 1 met the diagnostic criteria for DM only because of an elevated Hemoglobin A1C level. Therefore, a total of 11/75 (14.7%) of subjects had at least one criterion for established or presumptive DM.
- A prior diagnosis of hypertension was present in 16.9%, and a prior diagnosis of hyperlipidemia was present in 19.7% of subjects at protocol Time 0. Blood tests at protocol Time 0 revealed an elevated cholesterol level in 1.3%, a low HDL level in 37.3%, an elevated LDL level in 2.7%, an elevated cholesterol/HDL ratio in 14.7%, and an elevated triglyceride level in 10.7%.

- Fasting glucose, hemoglobin A1C, and blood lipid panels were repeated at protocol Months 3, 6, and 12. On an intention-to-treat basis, prescribing bi-level PPV did not improve on any of these laboratory studies relevant to the metabolic syndrome.

KEY RESEARCH ACCOMPLISHMENTS

- Demonstrated that home-based sleep testing and overnight tc-pCO_2/SpO_2 monitoring can be done safely, without undue risk of equipment damage or an unacceptable frequency of failed studies.
- Home-based sleep testing demonstrated a very high prevalence of both obstructive and central sleep apnea in patients with spinal cord injury, effectively reproducing the results of facility-based sleep studies.
- Our modified scoring strategy avoids mis-classification of central hypopneas as obstructive events in a subgroup of SCI patients.
- Overnight tc-pCO_2/SpO_2 monitoring demonstrates a high prevalence of sleep-related hypercapnia in patients with spinal cord injury.
- The severity of obstructive sleep apnea correlates with neck circumference, but <u>does not</u> correlate with the level or duration of spinal cord injury, forced vital capacity, or symptoms.
- The severity of central sleep apnea correlates with use of sedating medications and to the severity of obstructive sleep apnea.
- The severity of nocturnal hypercapnia correlates poorly with clinical features or pulmonary function. While awake pCO_2 is slightly higher in patients with nocturnal hypercapnia and is a weak predictor of NH, there is too much overlap between subjects with vs. without NH for daytime pCO_2 to be a clinically useful predictor for most subjects.
- The presence or absence of nocturnal oxygen desaturation is not an accurate predictor for the presence or absence nocturnal hypercapnia. Likewise, nocturnal hypercapnia cannot predict oxygen desaturation.
- Adherence to noninvasive ventilation is often suboptimal and highly variable. Expiratory pressure levels have some predictive value for adherence in patients with OSA alone (using BiPAP-auto), while inspiratory pressure settings predict adherence for patients using BiPAP/AVAPS for SDB with hypercapnia.
- Prescribing bi-level PPV for SDB ± hypercapnia appears to reduce symptoms of blood pressure instability.
- Despite what we would traditionally view as suboptimal adherence to treatment, bi-level PPV leads to short-term qualitative benefits, as reflected in quality of life surveys.
- We do not see any short-term benefits regarding laboratory parameters of glucose intolerance or dyslipidemia.

REPORTABLE OUTCOMES
Manuscripts, Abstracts, Patent Applications
One manuscript describing the preliminary data for this project was published (Appendix 1), and we published an interim report of our sleep study results in abstract form (Appendix 2). The final report has been accepted for publication as is now in press (Appendix 3). The report on device adherence and short-term benefits of treatment is now submitted for publication (Appendix 4).

CONCLUSIONS
Our data already indicate that our home-based testing strategy can be a practical, convenient, and low-cost approach for diagnosing sleep-related breathing disorders in SCI patients and informing the indications for noninvasive ventilatory support. Most SCI patients have OSA, and it is best predicted by neck

circumference. Central sleep apnea is also present in a significant proportion of subjects. Nocturnal hypercapnia is also present in approximately 1/4 of SCI patients. Clinical parameters, pulmonary function testing, and the presence/absence of oxygen desaturation are of no value in predicting nocturnal hypercapnia. Adherence to treatment with bi-level PPV treatment is highly variable and generally poor. Adherence cannot be predicted by clinical parameters, but the average expiratory pressure has some predictive value for patients treated with BiPAP-auto, and the average inspiratory pressure has predictive value for treatment with BiPAP/AVAPS. Future studies will be necessary to determine whether this is a causal relationship, or whether the pressures are indirectly related to device use in a non-causal way. Our data suggests that on an intention-to-treat basis, bilevel-PPV may lead to significant reductions in blood pressure instability (autonomic dysreflexia and orthostatic hypotension). We have also seen short-term benefits of treatment as reflected in the quality of life surveys, but no improvement in laboratory results related to dyslipidemia or glucose tolerance. Overall, our conclusions are limited by the numbers of subjects with no SDB who remained in-protocol throughout the entire study, and also by the relatively large number of subjects who withdrew from the study protocol after Time 0.

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Bauman KA, Kurili A, Schotland HM, Rodriguez GM, Chiodo AE, Sitrin RG. Positive Airway Pressure Therapy for Sleep Disordered Breathing in Individuals with Spinal Cord Injury: Adherence and Short-Term Benefits   In submission

ORIGINAL ARTICLE

Home-Based Overnight Transcutaneous Capnography/Pulse Oximetry for Diagnosing Nocturnal Hypoventilation Associated With Neuromuscular Disorders

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Abstract

Objective: To determine the utility of home-based, unsupervised transcutaneous partial pressure of carbon dioxide (tc-P_{CO_2}) monitoring/oxygen saturation by pulse oximetry (S_{PO_2}) for detecting nocturnal hypoventilation (NH) in individuals with neuromuscular disorders.

Design: Retrospective case series analyzed consecutively.

Setting: Multidisciplinary neuromuscular respiratory failure (NMRF) clinic at an academic institution.

Participants: Subjects (N=35, 68.6% men; mean age, 46.9y) with spinal cord injury (45.7%) or other neuromuscular disorders underwent overnight tests with tc-P_{CO_2}/S_{PO_2} monitoring. Fifteen (42.9%) were using nocturnal ventilatory support, either bilevel positive airway pressure (BiPAP) or tracheostomy ventilation (TV).

Interventions: A respiratory therapist brought a calibrated tc-P_{CO_2}/S_{PO_2} monitor to the patient's home and provided instructions for data collection during the subject's normal sleep period. Forced vital capacity (FVC), body mass index (BMI), and exhaled end-tidal P_{CO_2} (ET-P_{CO_2}) were recorded at a clinic visit before monitoring.

Main Outcome Measures: Detection of NH (tc-P_{CO_2} ≥50mmHg for ≥5% of monitoring time). Data were also analyzed to determine whether nocturnal oxygen desaturation (S_{PO_2} ≤88% for ≥5% of monitoring time), FVC, BMI, or daytime ET-P_{CO_2} could predict the presence of NH.

Results: NH was detected in 18 subjects (51.4%), including 53.3% of those using BiPAP or TV. NH was detected in 43.8% of ventilator-independent subjects with normal daytime ET-P_{CO_2} (present for 49.4%±31.5% [mean ± SD] of the study period), and in 75% of subjects with an elevated daytime ET-P_{CO_2} (present for 92.3%±8.7% of the study period). Oxygen desaturation, BMI, and FVC were poor predictors of NH. Only 3 attempted monitoring studies failed to produce acceptable results.

Conclusions: Home-based, unsupervised monitoring with tc-P_{CO_2}/S_{PO_2} is a useful method for diagnosing NH in NMRF.

Archives of Physical Medicine and Rehabilitation 2013;94:46-52

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Neuromuscular respiratory failure (NMRF) is often managed with noninvasive ventilation (NIV) to forestall progression of hypercapnia and to relieve dyspnea. Because nocturnal hypoventilation (NH) generally precedes daytime hypercapnia, the first indication for NIV may be transient rises in the partial pressure of carbon dioxide (P_{CO_2}) during sleep, even in the absence of obstructive sleep apnea (OSA).[1-3] Recognizing NH early may have particular value, because any nocturnal P_{CO_2} reaching ≥50mmHg marks a high probability of requiring NIV within 2 years.[4] Additionally, initiating NIV based on symptomatic daytime hypercapnia results in improved mortality and quality of life in amyotrophic lateral sclerosis (ALS).[5] A practical, cost-effective method for early recognition of NH has yet to emerge. Currently available

approaches include correlating NH with lung function parameters,[1,6,7] polysomnograms (PSGs) with exhaled P_{CO_2} monitoring,[8] and arterial blood gas monitoring.

Current methods are limited in their ability to predict or detect NH, and to determine the proper timing for initiating NIV. Pulmonary function parameters such as forced vital capacity (FVC) can predict the need for NIV in certain neuromuscular conditions, but they do not reliably predict hypercapnia.[1,6,7] Nocturnal P_{CO_2} monitoring, either by arterial blood gas or end-tidal P_{CO_2} (ET-P_{CO_2}) measurements, generally requires an inpatient study or an overnight stay in a sleep laboratory. It is problematic to assess outpatients with neuromuscular disorders for NH, as sleep laboratories often are ill-equipped to accommodate their special needs. Barriers to access and the inability to accommodate skilled caregivers impose daunting obstacles that, in our experience, often cause patients to refuse overnight stays in sleep laboratories. Likewise, once nocturnal NIV is initiated, there are no established methods for longitudinal home-based monitoring to determine the effectiveness of positive pressure ventilation in achieving normocapnia.

We hypothesized that the barriers to performing PSGs have led to underrecognition of NH in patients with neuromuscular disorders. In this study, we report our experience with using a monitor that measures transcutaneous P_{CO_2} (tc-P_{CO_2}) and oxygen saturation by pulse oximetry (S_{PO_2}) for unsupervised overnight studies in the home setting to detect NH in individuals with a variety of neuromuscular disorders.

Methods

Informed consent

Permission for retrospective analysis of patient medical records was granted for this study by the institutional review board. The monitoring studies that were reviewed were performed between December 2009 and June 2011.

Participants

The study population consisted of patients seen at a multidisciplinary clinic for treatment of NMRF. These patients are managed jointly by a pulmonologist and a physical medicine and rehabilitation specialist. The motor deficit of patients with spinal cord

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List of abbreviations:

ALS	amyotrophic lateral sclerosis
BiPAP	bilevel positive airway pressure
BMI	body mass index
ET-P_{CO_2}	end-tidal partial pressure of carbon dioxide
FVC	forced vital capacity
NH	nocturnal hypoventilation
NIV	noninvasive ventilation
NMRF	neuromuscular respiratory failure
OSA	obstructive sleep apnea
P_{CO_2}	partial pressure of carbon dioxide
PSG	polysomnogram
SCI	spinal cord injury
S_{PO_2}	oxygen saturation by pulse oximetry
tc-P_{CO_2}	transcutaneous partial pressure of carbon dioxide
TV	tracheostomy ventilation

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injury (SCI) was defined according to the International Standards for the Neurological Classification of Spinal Cord Injury.[9]

Home-based monitoring

Monitoring was performed only when the patients were clinically stable for at least 4 weeks. A respiratory therapist brought a Sen-Tec Digital Monitor[a] to the patient's home on the day of the study. This monitor measures and records tc-P_{CO_2}, S_{PO_2}, and heart rate. The therapist calibrated the monitor and attached the skin probe below the clavicle. The patient/caregivers were instructed to start recording at the beginning of the overnight sleep period, and to turn the monitor off when the patient awoke the following morning. The data were then downloaded and analyzed by V-STATS software,[a] using automated drift-correction of the P_{CO_2} signal. The manufacturer's reported resolution is 1mmHg for P_{CO_2} and 1% for S_{PO_2}. With the use of this device to compare drift-corrected tc-P_{CO_2} with arterial P_{CO_2} in a sleep laboratory setting, there was close correlation ($R=.946$) and agreement between measurements (range of differences, -4.9 to $+6.5$mmHg).[10] Bland-Altman analysis demonstrated that the discrepancy was >7.5mmHg in only 1% of measurement pairs.[10]

Pulmonary function testing

Spirometry was performed by a pulmonary function laboratory equipped with MedGraphics spirometers.[b] Studies were performed according to the guidelines published by the American Thoracic Society and European Respiratory Society.[11] Predicted values were calculated according to standard reference equations.[12]

ET-P_{CO_2} measurements

A Tidal Wave 715A monitor[c] was used to measure ET-P_{CO_2} during outpatient evaluations when the patients were clinically stable.

Statistics

Comparisons between groups were made by t tests for continuous variables and chi-square tests for categorical variables. Simple logistic regression was used to predict the odds of NH. P values less than .05 were considered significant. All data analysis was performed on SAS software, version 9.2.[d]

Results

The characteristics of the study population are summarized in table 1. The patients had a mean age ± SD of 46.9±16.6 years (range, 20−75y), and 68.6% were men. Sixteen patients (45.7%) had SCI, and 68.8% of these had motor deficits at or above the C5 level. The mean interval ± SD since SCI was 13.5±10.8 years (range, 2−37y). Of the 19 patients who had neuromuscular disorders other than SCI, 5 had multiple sclerosis, 2 each had ALS, cerebral palsy, or Duchenne muscular dystrophy, and 6 had other miscellaneous diagnoses. Fifteen patients (42.9%) were already using nocturnal ventilatory support: bilevel positive airway pressure (BiPAP)[10] or mechanical tracheostomy ventilation (TV).[5]

The indications for overnight monitoring are summarized in table 2. The most common reason for the study, in 16 cases

Table 1   Patient characteristics (N=35)

Age (y)	46.9±16.6 (20−75)
Sex	
Men	24 (68.6)
Women	11 (31.4)
Diagnosis	
SCI	16 (45.7)
Neuromuscular disease/other	19 (54.3)
Multiple sclerosis	5
ALS, Duchenne muscular dystrophy, myotonic dystrophy, cerebral palsy	2 each
Scoliosis, Kennedy's disease, obesity hypoventilation, myelocele, congenital central hypoventilation, traumatic brain injury	1 each
FVC (% predicted)	36±11.8 (17−58)
BMI (kg/m^2)	26.4±7.2 (13−48.3)
Duration of overnight monitoring (min)	496.8±106.6 (230−664)

NOTE. Values are mean ± SD (range) or n (%). Duration of monitoring excluded 2 studies in which monitoring was not terminated as instructed.

was ≥50mmHg was 49.4%±31.5% (mean ± SD), ranging from 11% to 97%. Peak P_{CO_2} values ranged from 54 to 58mmHg. Among the 4 patients with daytime hypercapnia and not using BiPAP/TV, 3 (75%) had NH, and the P_{CO_2} was ≥50mmHg for 92.3%±8.7% (mean ± SD) of the study time (range, 80%−99%). Peak P_{CO_2} values were 60 to 71mmHg.

Fifteen (42.9%) of the patients were using BiPAP or TV at the time of the overnight study. In all cases, the primary indication for BiPAP/TV was respiratory failure and not OSA. Most patients (60%) using BiPAP/TV had a diagnosis of a neuromuscular disorder other than SCI, while only 27.6% had SCI (P=.05). NH was detected in 8 (53.3%) of these patients. The P_{CO_2} was ≥50mmHg for 74.3%±27.6% (mean ± SD) of the study time (range, 10%−100%), and peak P_{CO_2} values ranged from 56 to 143mmHg.

Next, we sought to determine whether clinical indicators such as body mass index (BMI), FVC, or nocturnal oxygen desaturation could predict the presence of NH. The BMI was measured within 3 months before the overnight study. Including all patients, the BMI in patients with NH confirmed by the overnight study was 27.4±8.5kg/m^2 compared with 25.3±5.8kg/m^2 without NH (P=.40) (table 3). The FVC was measured within 6 months of the overnight study in 26 patients (74.3%). Another 6 studies were excluded from this analysis (3 unable to perform spirometry, and not attempted in 3 because of disease progression). The FVC in those with NH was 35.2%±12.1% predicted, compared with 36.6%±12.3% in those without NH (P=.77). Scatterplots of the BMI, motor level, and FVC provide more detailed individual information for the SCI group (fig 1). Lastly, nocturnal oxygen desaturation (Spo_2 <88% for >5% of study time) was found in 6 patients (33.3%) with, and in 5 (29.4%) without NH (P=.80). We also applied simple logistic regression analyses to determine whether these clinical and laboratory features could predict NH (table 4). Including all studies, the only predictor of NH is elevated daytime ET-P_{CO_2} (odds ratio=1.21; 95% confidence interval, 1.04−1.41; P=.01). Because nocturnal ventilatory support probably prevented some instances of NH or oxygen desaturation, we performed separate simple logistic regressions for patients not using nocturnal ventilatory support and those using nocturnal BiPAP/TV. Only in the latter group did daytime ET-P_{CO_2} predict the likelihood of NH (see table 4). We note that the present study included patients with a variety of underlying diagnoses, and only patients with SCI were represented in significant numbers. Future studies focusing on specific underlying diagnoses will be necessary to determine whether reliable clinical predictors for NH can be identified for specific neuromuscular disorders.

(45.7%), was to determine whether NH was present in patients with normal daytime ET-P_{CO_2} and moderate-severe restrictive ventilatory defects on spirometry, but not using nocturnal ventilatory support. In 4 cases (12.1%), monitoring was performed to determine the severity of NH in patients known to have daytime hypercapnia (ET-P_{CO_2}, 47−55mmHg), but not using ventilatory support. Fifteen (42.9%) studies were performed on patients using BiPAP/TV to determine whether NH was adequately controlled.

Of the 38 overnight studies, 3 (8.6%) were determined to be unacceptable, either because of a technical problem (detached probe), an unusually short sleep time, or an unacceptably high P_{CO_2} signal artifact. Therefore, a total of 35 studies in 35 individuals are included in the final analysis. In the valid studies, data were recorded for a mean of 496.8 minutes (see table 1). There were no adverse events or patient complaints associated with the monitoring procedure.

Among the 16 normocapneic patients who were not using BiPAP/TV, NH was confirmed in 7, for an overall yield of 43.8% (see table 2). The percent of the study time during which the P_{CO_2}

Table 2   Prevalence and severity of nocturnal hypercapnia, stratified by indication for monitoring

Indication for Overnight tc-P_{CO_2}/Pulse Oximetry Monitoring	NH	% of Monitoring Time With tc-P_{CO_2} ≥50mmHg	Peak P_{CO_2} (mmHg)
I. Determine whether nocturnal hypercapnia or oxygen desaturation is present (patients with daytime ET-P_{CO_2} <47mmHg and not using nocturnal ventilatory support) n=16 (45.7%)	7 (43.8)	49.4±31.5 (11−97)	55.6±1.9 (54−58)
II. Determine the severity of nocturnal hypercapnia or oxygen desaturation (patients with daytime ET-P_{CO_2} ≥47mmHg and not using nocturnal ventilatory support) n=4 (12.1%)	3 (75)	92.3±8.7 (80−99)	66.1±4.6 (60−71)
III. Determine the effectiveness of TV/BiPAP in preventing nocturnal hypercapnia or oxygen desaturation n=15 (42.9%)	8 (53.3)	74.3±27.6 (10−100)	76.5±9.7 (56−143)

NOTE. Values are n (%) or mean ± SD (range). NH = tc-P_{CO_2} ≥50mmHg for ≥5% of monitoring time.

Table 3 Predictors of NH

Variables	All Patients (N=35)	Patients Without NH (n=17)	Patients With NH (n=18)	P^*
Age (y)	46.9±16.6	45.4±17.6	48.4±16.0	.60
Sex				
Men	24 (68.6)	11 (64.7)	13 (72.2)	.63
Women	11 (31.4)	6 (35.3)	5 (27.8)	
Diagnosis				
SCI	16 (45.7)	6 (35.3)	10 (55.6)	.23
NM/other	19 (54.3)	11 (64.7)	8 (44.4)	
Use of BIPAP or TV	15 (42.9)	7 (41.2)	8 (44.4)	.85
BMI (kg/m^2)	26.4±7.3	25.3±5.8	27.4±8.5	.40
FVC (% predicted)	36.0±12.0	36.6±12.3	35.2±12.1	.77
Daytime Spo_2 (%)	96.4±2.2	97.1±1.95	95.8±2.3	.10
Presence of nocturnal oxygen desaturation	11 (31.4)	5 (29.4)	6 (33.3)	.80
Daytime $ET\text{-}Pco_2$ (mmHg)	43.9±5.5	41.3±4.6	46.3±5.4	.006
Daytime $ET\text{-}Pco_2$ >47mmHg	14 (40)	4 (23.5)	10 (55.6)	.05

NOTE. Values are mean ± SD, n (%), or as otherwise indicated. NH = tc-Pco_2 ≥50mmHg for ≥5% of monitoring time. Oxygen desaturation defined as Spo_2 ≤88% for ≥5% of monitoring time. Statistical analysis: comparisons between groups were made by *t* tests for continuous variables and χ^2 tests for categorical variables.
Abbreviation: NM/other, neuromuscular disorders other than SCI.
  * *P* values are for comparisons of patients with NH vs without NH.

Discussion

NH is a well-recognized complication of many neuromuscular disorders. Current diagnostic studies are limited for this population because of both study characteristics and logistics. Our data highlight that in patients with neuromuscular disorders, NH is common and underrecognized, and that easily accessible parameters such as BMI, FVC, and oxygen desaturation do not reliably predict its presence. We also demonstrate that patients receiving home nocturnal ventilation for NMRF frequently do not achieve normocapnia. These findings establish a role for home-based, unsupervised overnight tc-Pco_2/Spo_2 monitoring in the care of patients with NMRF.

Physicians recognize that they should be vigilant for emerging NMRF,[2,3,13] but it can develop over any time frame as a result of worsening of the underlying disorder, age-related decline in lung
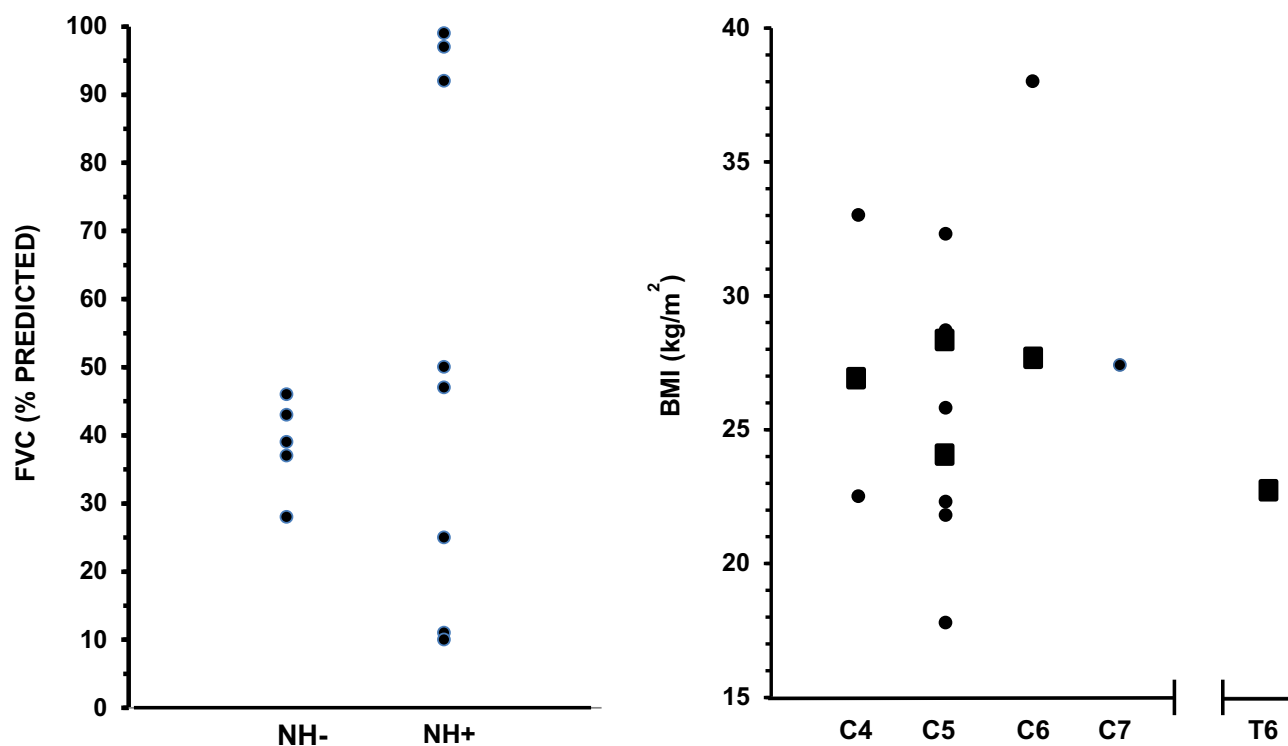
Fig 1 Characteristics of patients with SCI. Left: Scatterplot of the FVC, expressed as % predicted, stratified by the absence (NH−) or presence (NH+) of nocturnal hypoventilation determined by overnight transcutaneous capnography. Right: Scatterplot of the distribution of motor deficit level and BMI, with each symbol representing a single patient: ■, NH−; ●, NH+.

Table 4 Simple logistic regressions for prediction of NH

Patient Variables	All Patients			No Nocturnal Ventilatory Support (n=20)			Using Nocturnal Ventilatory Support (n=15)		
	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI
Age	.59	1.01	0.97–1.05	.82	0.99	0.94–1.05	.32	1.03	0.97–1.10
Male sex	.63	1.42	0.34–5.94	.34	2.67	0.36–19.7	.72	0.67	0.08–5.88
BMI	.40	1.04	0.95–1.15	.71	1.03	0.89–1.19	.44	1.06	0.92–1.21
SCI diagnosis	.23	2.29	0.59–8.94	.37	2.33	0.37–14.6	.33	3.60	0.28–46.4
FVC	.76	0.99	0.93–1.06	.93	1.00	0.93–1.08	.59	0.96	0.82–1.12
Sp_{O_2}	.11	0.74	0.52–1.06	.73	1.13	0.57–2.27	.07	0.62	0.37–1.03
$ET\text{-}P_{CO_2}$	.012	1.21	1.04–1.41	.14	1.17	0.95–1.45	.04	1.25	1.01–1.56

NOTE. OR = fold-increase in odds of having NH for each 1-point rise for a continuous variable, or yes vs no for a categorical variable. NH = tc-P_{CO_2} ≥50mmHg for ≥5% of monitoring time. FVC studies excluded if performed >6 months before P_{CO_2}/Sp_{O_2} monitoring: all patients, n=26; no ventilatory support, n=16; using ventilatory support, n=10.
Abbreviations: CI, confidence interval; OR, odds ratio.

function, worsening scoliosis, chest wall ankylosis, and the cumulative effects of respiratory infections.[3] In SCI, most patients remain stable after liberation from ventilatory support during their initial hospitalization, while a decline in pulmonary function has been documented in some patients as much as 10 to 20 years later.[14,15] Likewise, late development of hypercapnia has been described.[16] Therefore, patients are often living at home when their pulmonary function is declining. By this time, they are often highly resistant to hospitalization, or to overnight stays in a sleep laboratory where their specialized needs are difficult to accommodate.

The decision to begin NIV is complex, as it involves several interrelated problems, any of which may be an indication for ventilatory support.[2,3,17] While NIV does not improve pulmonary function or respiratory muscle strength in the long-term,[18,19] it does provide short-term relief of dyspnea and enables the patient to sleep without nocturnal P_{CO_2} retention or frequent arousals. It remains uncertain whether clinical outcomes can be optimized by using spirometry or indices of respiratory muscle strength as the primary indicator for starting NIV.[1-3,7,8,20,21] The complexity of this problem is compounded by the observation that the physiologic status of patients at the onset of NIV may vary, depending on the underlying diagnosis.[22] In the present study, FVC was a poor predictor of NH in all patient groups (see table 4). Thus, while spirometry may predict the utility of NIV for some patients, it does not follow that it will specifically identify patients with nocturnal hypercapnia. NIV may also be initiated to interrupt an escalating cycle of hypercapnia, oxygen desaturation, atelectasis, and recurrent infections. Any degree of NH can predict progression to requiring NIV support within months.[4] Later intervention, when symptomatic daytime hypercapnia has developed, has been shown to improve short-term mortality and quality of life in ALS.[5] It remains to be determined whether these clinical benefits are conferred, or even magnified, if NIV is begun while hypercapnia only occurs during sleep. If so, early detection of hypercapnia by overnight monitoring would clearly be preferable to daytime assessments.

Thus far, transcutaneous capnography has been used mostly in inpatient settings.[10,23-27] It has also been an effective tool for managing acute-on-chronic respiratory failure with BiPAP,[28] and as an adjunct to PSGs performed in a sleep laboratory.[10] Our study confirms that recording transcutaneous capnography, in this case the SenTec Digital Monitor, can also be used effectively for unsupervised overnight monitoring in the outpatient setting.

Home-based, continuous tc-P_{CO_2} monitoring has several advantages. First, it may be the only method for assessing patients who refuse testing in a sleep laboratory. Second, home-based testing may provide a more authentic assessment during the usual sleep patterns of patients, whereas a sleep laboratory setting could undermine the patients' normal sleep by disrupting their schedule, providing an unfamiliar or unsuitable bed, or altering their use of medications or alcohol. Spot checks of P_{CO_2} by any method would be susceptible to sampling error if hypercapnia is transient. Continuous monitoring of ET-P_{CO_2} in the home may require frequent adjustments by a technician, which may disrupt sleep and add considerably to the cost of the study. Monitoring P_{CO_2} levels without disturbing the patient's sleep would be critical to assess NH and properly titrate BiPAP. Lastly, ET-P_{CO_2} may not accurately reflect the partial pressure of arterial carbon dioxide in the presence of mask leakage or parenchymal lung disease.[24,29] Home-based continuous monitoring by transcutaneous capnography would circumvent these problems.

The last, and least studied, indication for beginning NIV is to prevent adverse systemic effects of hypercapnia. There is substantial evidence that OSA confers greater risks for mortality, myocardial infarction, hypertension, stroke, and glucose intolerance.[30-32] Presently, we do not know the extent to which hypercapnia in the absence of OSA is associated with these same risks. If the systemic effects of NH are similar to those of OSA, then early recognition of NH should be preferable to waiting until daytime hypercapnia develops. It is notable that in our patients, NH could not be predicted by nocturnal oxygen desaturation or the severity of pulmonary restriction (see tables 3 and 4), supporting the concept that while dyspnea, atelectasis, and nocturnal hypercapnia are highly interrelated, none of these can stand alone as the justification for starting NIV.[17] Thus, overnight transcutaneous capnography provides complementary data that can facilitate the decision-making process to start NIV. In addition, overnight transcutaneous capnography/pulse oximetry can be used to monitor the effectiveness of BiPAP or mechanical ventilator settings for the treatment of NMRF.

Study limitations

We acknowledge several weaknesses and limitations to this study. First, the retrospective design may have significantly influenced

the reported prevalence of NH. Most of the studies we performed were part of an initial assessment at a multidisciplinary clinic for management of NMRF, occurring at a point when most patients already had severe pulmonary restriction. The yield of these studies can be expected to vary considerably, depending on the patient mix and the timing of the studies. Next, it is critical to note that our study specifically addresses NH and not OSA, so tc-P_{CO_2} monitoring cannot be used as a substitute for PSGs, just as PSGs are generally configured to diagnose OSA/central sleep apnea, and not NH.[33] Depending on the underlying diagnosis, OSA and NH may coexist frequently, so neither overnight tc-P_{CO_2} monitoring nor standard PSG alone can be expected to fully characterize sleep-related breathing disorders. We cannot compare the reliability, accuracy, or cost-effectiveness of the SenTec monitor used in the present study with similar devices from other manufacturers. Lastly, a cost-benefit analysis will remain incomplete until the long-term costs of ventilatory support initiated because of this monitoring strategy, as well as the long-term health benefits/risks, can be quantitated.

Conclusions

Home-based overnight monitoring with transcutaneous capnography/pulse oximetry is a practical method for detecting NH in patients with SCI. Nocturnal hypercapnia is common, even in patients with normal daytime P_{CO_2} levels, and in patients already receiving ventilatory support. Nocturnal hypercapnia cannot be predicted accurately by recent spirometry, BMI, or nocturnal oxygen desaturation.

Suppliers

a. SenTec, Ringstrasse 39, CH-4106 Therwil BL, Switzerland.
b. Medgraphics corporation, 350 Oak Grove Pkwy, St. Paul, MN 55127.
c. Philips Respironics, Philips Healthcare, 3000 Minuteman Rd, Andover, MA 01810-1099.
d. SAS Institute Inc, 100 SAS Campus Dr, Cary, NC 27513.

Keywords

Blood gas monitoring, transcutaneous; Home care services, hospital-based; Hypoventilation; Neuromuscular diseases; Rehabilitation; Sleep apnea syndromes

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Home-Based Diagnosis of Sleep-Disordered Breathing Complicating Spinal Cord Injury FREE TO VIEW

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▶ Author and Funding Information

TextSize: A A A

Article

Abstract

SESSION TITLE: Sleep Posters

SESSION TYPE: Original Investigation Poster

PRESENTED ON: Wednesday, October 30, 2013 at 01:30 PM - 02:30 PM

PURPOSE: Individuals with spinal cord injury (SCI) commonly suffer from sleep-disordered breathing due to obstructive sleep apnea (OSA) or nocturnal hypoventilation (NH) from respiratory muscle weakness. Standard polysomnograms (PSG) reliably diagnose OSA, but carbon dioxide (pCO_2) measurements are not performed routinely, and SCI patients often have difficulty accessing sleep centers. We sought to determine the prevalence of OSA and NH in SCI patients, utilizing concurrent in-home PSG and transcutaneous capnography. Additionally, we examined the reliability of common clinical predictors for OSA or NH.

METHODS: Adults with C1-T6 SCI were studied prospectively. Anthropometric data, Epworth sleepiness scale (ESS), and spirometry were measured at baseline. An in-home, unsupervised overnight PSG (Stardust II class III system, Phillips Respironics) was performed concurrently with transcutaneous pCO_2/SpO_2 monitoring (SenTec AG, Therwil, Switzerland).

RESULTS: 35 studies were performed successfully. 7 PSG and 4 capnography studies were repeated due to technical problems. 31 subjects (88.6%) had OSA, as defined by an obstructive apnea hypopnea index (OAHI) of ≥ 5 events/hr of recording time (mean 20.7; range 5.4-60). Twelve (34.3%) subjects had NH (transcutaneous pCO_2 ≥ 50mmHg for ≥ 5% study time) for a mean of 31.6% of the study time (range 5-99%). Oxygen desaturation (SpO_2 ≤ 88% for ≥ 5% of study time) was detected in 7 (20%). The OAHI correlated with neck circumference (p = 0.004) and waist circumference (p = 0.028). ESS, BMI, and forced vital capacity (FVC) did not correlate with OAHI or NH.

CONCLUSIONS: Home-based PSG/transcutaneous capnography is an effective approach for diagnosing OSA and NH in SCI patients. OSA is common and under-recognized. Neck and waist circumference correlate with the severity of OSA, while ESS, FVC and O2 desaturation do not.

CLINICAL IMPLICATIONS: Home-based unsupervised PSG/transcutaneous capnography can facilitate recognition of OSA and NH, removing the obstacles associated with facility-based PSG. Future implications could include early institution of noninvasive ventilation with improved quality of life and decreased morbidity.

DISCLOSURE: The following authors have nothing to disclose: Kristy Bauman, Armando Kurili, Gianna Rodriguez, Anthony Chiodo, Helena Schotland, Robert Sitrin

No Product/Research Disclosure Information

ORIGINAL RESEARCH

Simplified Approach to Diagnosing Sleep-Disordered Breathing and Nocturnal Hypercapnia in Individuals With Spinal Cord Injury

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Abstract

Objective: To evaluate a strategy of home-based testing to diagnose sleep-disordered breathing and nocturnal hypercapnia in individuals with spinal cord injury (SCI).

Design: Case series.

Setting: Referral center.

Participants: Adults with C1-T6 SCI (N=91). Individuals were eligible if ≥18 years old, with SCI of ≥3 months' duration, living within 100 miles of the study site, and not meeting exclusion criteria. Of the 161 individuals recruited from the SCI Model System database who were not enrolled, reasons were not interested in participating, change of location, prior positive pressure ventilation use, or medical contraindication. Ten individuals did not complete the study.

Interventions: Performance of an unsupervised home sleep apnea test combined with transcutaneous partial pressure of carbon dioxide/oxygen saturation by pulse oximetry monitoring.

Main Outcome Measures: Prevalence of sleep-disordered breathing and nocturnal hypercapnia. Clinical and physiological variables were examined to determine which, if any, correlate with the severity of sleep-disordered breathing.

Results: Obstructive sleep apnea (OSA) was found in 81.3% of individuals, central sleep apnea (CSA) was found in 23.8%, and nonspecific hypopnea events, where respiratory effort was too uncertain to classify, were present in 35%. Nonspecific hypopnea events correlated strongly with CSA but weakly with OSA, suggesting that conventional sleep apnea test scoring may underestimate central/neuromuscular hypopneas. Nocturnal hypercapnia was present in 28% and oxygen desaturation in 18.3%. Neck circumference was the primary predictor for OSA, whereas baclofen use and obstructive apnea/hypopnea index weakly predicted CSA. Awake transcutaneous partial pressure of carbon dioxide and CSA were only marginally associated with nocturnal hypercapnia.

Conclusions: Unsupervised home sleep apnea testing with transcutaneous capnography effectively identifies sleep-disordered breathing and nocturnal hypercapnia in individuals with SCI.

Archives of Physical Medicine and Rehabilitation 2015;■:■■■-■■■

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Individuals with spinal cord injury (SCI) commonly have sleep-disordered breathing, particularly obstructive sleep apnea (OSA).[1-4] Individuals with SCI may also experience central sleep apnea (CSA) or nocturnal hypoventilation due to reduced ventilatory drive during sleep and/or respiratory muscle paralysis.[5] In the general population, OSA is associated with impaired cognitive function and increased risk of myocardial infarction, stroke, congestive heart failure, and the "metabolic syndrome."[6-12] Poor sleep quality is common in SCI, but we know little about its consequences.[13,14] Furthermore, it is not known whether nocturnal hypercapnia in SCI confers the same risks as OSA, although nocturnal hypercapnia portends progression of respiratory failure

in several neuromuscular disorders.[15] Obesity, cardiovascular morbidity, and diabetes are common in SCI, raising the possibility that unrecognized sleep-disordered breathing contributes to these comorbidities.[16-19]

Polysomnography (PSG) reliably diagnoses sleep apnea, but partial pressure of carbon dioxide (Pco_2) measurements are not routine, so nocturnal hypercapnia may go undetected. Studies performed in sleep laboratories have shown that 40% to 60% of individuals with SCI have OSA.[1-4] Individuals with SCI often forgo facility-based PSG because of barriers such as inadequate wheelchair accessibility and accommodations for caregivers. It is probable that sleep-disordered breathing is underrecognized in individuals with SCI, thereby denying them appropriate treatment with continuous or bilevel positive pressure ventilation (PPV). Recent technological advances enable us to collect valid data from home-based studies, circumventing the logistical obstacles associated with facility-based PSG. The potential advantages of home-based testing include improved convenience/acceptance by individuals and families as well as reduced cost. The purpose of this study was to determine whether sleep-disordered breathing and nocturnal hypercapnia could be diagnosed reliably and efficiently by home-based testing in individuals with SCI. In addition, we sought to determine whether clinical factors could reliably predict the severity of sleep-disordered breathing.

Methods

Permission was provided by the Institutional Review Board of the University of Michigan (project no. HUM00051504). The study was performed between March 1, 2012 and November 15, 2014. Eligibility was determined by reviewing the University of Michigan SCI Model System database, which includes approximately 90% of individuals with SCI in the region. Individuals were eligible if ≥18 years old, with C1-T6 SCI (all American Spinal Injury Association grades of motor impairment) of ≥3 months' duration, and lived within 100 miles of the study site. Exclusion criteria included inability to provide informed consent, comorbid condition that limited life expectancy to ≤1 year, active duty military personnel, ventilator dependence, and established diagnosis of sleep-disordered breathing, or prior use of noninvasive PPV, except during hospitalization ≥3 months before enrollment. Among those not enrolled, 61.7% were not interested in participating, 5.7% had moved beyond the maximum distance to the study site, 14.2% were ineligible because of prior PPV use or presence of a tracheostomy tube, and 9.2% for other medical reasons. After an observation phase of 4 months to establish stability, the clinical assessment, home

List of abbreviations:

CSA	central sleep apnea
FVC	forced vital capacity
HSAT	home sleep apnea test
O-AHI	obstructive apnea/hypopnea index
OSA	obstructive sleep apnea
Pco_2	partial pressure of carbon dioxide
PPV	positive pressure ventilation
PSG	polysomnography
SCI	spinal cord injury
Spo_2	oxygen saturation by pulse oximetry
tc-Pco_2	transcutaneous partial pressure of carbon dioxide

sleep apnea test (HSAT), and transcutaneous partial pressure of carbon dioxide/oxygen saturation by pulse oximetry (tc-Pco_2/Spo_2) monitoring were performed. Weight, height, waist circumference, neck circumference, and body mass index were measured, and medical records were reviewed.[20,21] Spirometry was performed with MedGraphics Ultima spirometers[a] in the seated position according to the American Thoracic Society guidelines.[22] Motor level and completeness of SCI were determined according to the International Standards for the Neurological Classification of Spinal Cord Injury.[23]

HSATs were performed with the Stardust II (Type III) portable system,[b] which includes a nasal airflow sensor, a single thoracoabdominal piezoelectric belt to measure respiratory effort, and a pulse oximeter.[24] At the individual's home, the study coordinator placed the sensors and provided instructions regarding sensor placement in case they were dislodged during the study. After overnight tc-Pco_2 monitoring, data were downloaded to the manufacturer's software and the automated analysis was reviewed and rescored manually by a physician board−certified in sleep medicine (H.M.S.). The results were scored according to the 2007 American Academy of Sleep Medicine guidelines.[25] In addition, an alternate scoring strategy was developed. As in the American Academy of Sleep Medicine guidelines,[25] apneas were defined as ≥10-second periods of absent nasal airflow and hypopneas as ≥10 seconds of ≥50% reductions in airflow, relative to the preevent baseline. Events were classified as obstructive only if they were associated with stable or increasing respiratory effort, as determined by the amplitude of chest/abdominal movement; it criterion is now concordant with the 2015 American Academy of Sleep Medicine scoring manual.[26] The obstructive apnea/hypopnea index (O-AHI) is expressed as the number of obstructive events (apneas and hypopneas) per hour of recording time. If the period of reduced airflow was associated with decreasing chest/abdominal movement, it was interpreted as a nonspecific hypopnea event and excluded from the O-AHI. Events where baseline airflow was insufficient to measure a 50% reduction were classified as nonspecific hypopnea events. Furthermore, a reduction in Spo_2 was not used to score an obstructive event. An O-AHI of ≥5 events/h was chosen as the threshold for diagnosing OSA.

The study coordinator calibrated the SenTec Digital Monitor[c] immediately preceding each study. Monitoring of tc-Pco_2/Spo_2 was performed continuously through the individual's normal sleep period. Previous studies[27,28] support the accuracy of this device compared to arterial Pco_2 measurements. For this study, hypercapnia was defined as a tc-Pco_2 of ≥50mmHg for ≥5% of the recording time and oxygen desaturation was defined as Spo_2 of ≤88% for ≥5% of the recording time.

Statistical analysis

The distribution of continuous outcome variables was inspected using histograms. The O-AHI, CSA event, nonspecific hypopnea event, and percentage of monitoring time with tc-Pco_2≥50mmHg were found to be strongly skewed before and after covariate adjustment and were log-transformed before the analysis. Covariate effects for regression models with log-transformed dependent variables have a multiplicative interpretation and are reported as such. Marginal correlations were assessed using Pearson correlation coefficients. The Student t test was used for comparing group means. To develop predictive models, we identified a set of hypothesis-driven candidate predictor variables for each outcome

variable. For each candidate predictor variable, we assessed associations with the outcome variable using Pearson correlation coefficients. We then fit multiple linear regression models between each outcome measure and various sets of predictors using the LASSO method to guide variable selection. To address concerns about exploratory regression analyses, regression results were interpreted conservatively. All analyses were performed using R version 3.1 software.[d]

Results

Of 252 individuals contacted, 91 eligible individuals agreed to participate. After the observation phase of 4 months to establish clinical stability, the clinical assessment, HSAT, and tc-P_{CO_2}/S_{PO_2} monitoring were performed. Ten individuals did not complete the study (1 death, 1 prolonged hospitalization, 6 withdrawals, 2 were ineligible). Seventy-five men and 16 women (mean age, 47.7±12.3y; range, 20−75y) were enrolled. Individuals were 16.8±12.0 years postspinal cord injury with a range of 1 to 50 years. The distribution of SCI motor levels and American Spinal Injury Association grades are shown in figure 1. Sedating drugs prescribed at the time of the HSAT included baclofen in 78%, benzodiazepines in 43%, and ≥1 other sedating drugs (most commonly, analgesics) in 71%. Thirty-one percent were prescribed drugs in 2 classes, and 38% were prescribed drugs in all 3.

On the initial attempt, 15% of the HSATs and 21% of the tc-P_{CO_2}/S_{PO_2} studies provided insufficient data because of a detached probe (the tc-P_{CO_2}/S_{PO_2} studies), inadequate data from a single lead (1 nasal airflow, 1 S_{PO_2}), or equipment failure (2 Stardust II units replaced). Every tc-P_{CO_2}/S_{PO_2} study was repeated successfully, whereas in 2 studies a valid HSAT could not be performed. There were no instances of equipment damage or misuse. Monitoring was performed for 467.2±119.7 minutes (range, 197−809min). Adequate recording time was present in all the successful studies.

OSA was detected in 81.3% of individuals with an O-AHI of ≥5 events/h (fig 2A). Of the studies with abnormal results, the median O-AHI was 12.4 events/h (interquartile range, 9.0−25.5 events/h; range, 5.1−60 events/h). The severity of OSA varied

widely (see fig 2A). Of the 15 individuals without OSA, none had CSA and 4 had nocturnal hypercapnia.

Overall, there were 2.9 nonspecific hypopnea events/h (interquartile range, 0.3−7.9 events/h); however, in 35%, there were ≥5 events/h, and in 20%, ≥10 events/h (median, 22.5 events/h; interquartile range, 16.4−29.4 events/h) (see fig 2B). In no instance did the rescoring according to the 2007 American Academy of Sleep Medicine criteria reduce the scored events to <5 events/h.

CSA was found in 23.8%, and 10% had ≥15 CSA events/h (see fig 2C). Nocturnal hypercapnia was detected in 28% (fig 3A). As shown in Figure 3B, nocturnal hypercapnia was present for a median of 25% of the study time (interquartile range, 11%−72%; maximum, 100%) and the median maximum tc-P_{CO_2} was 56.7mmHg (interquartile range, 53.9−61mmHg; maximum, 95mmHg).

Several clinical and physiological variables were examined to determine which correlate with the severity of sleep-disordered breathing (appendix 1). Neck circumference is the strongest predictor; however, this positive association explained only 17% of the variation in O-AHI (not shown). After accounting for neck circumference, no other predictor was even weakly associated with the O-AHI. Sedating drugs and log O-AHI correlated with log CSA (see appendix 1). In multiple regression analysis, only baclofen use and O-AHI were predictive of CSA. The combination of multiple sedating drugs had minimal predictive value beyond use of any single class of drug (not shown). Unlike OSA, measurements of body shape had no association with CSA. Individuals with low O-AHI always had low levels of CSA, but individuals with high O-AHI had variable levels of CSA.

There is a strong correlation between CSA events and nonspecific hypopnea events (see appendix 1). The correlation between nonspecific hypopnea events and O-AHI, although statistically significant, is much weaker, suggesting that most nonspecific hypopnea events are central hypopneas. CSA events per hour accounted for 75% of the variation in nonspecific hypopnea events (not shown). Furthermore, neither nonspecific hypopnea events nor CSA events correlate with neck circumference. This supports the argument that the more stringent definition of OSA prevented misclassification of central events as obstructive, and therefore there was no overestimation of OSA. There was no relation between the presence of sleep-disordered breathing and the SCI level or American Spinal Injury Association grade.

Awake tc-P_{CO_2} was the only clinical variable with significant predictive value for nocturnal hypercapnia (appendix 2). The absence of any clinical predictors for nocturnal hypercapnia is further illustrated in figure 4, where parameters are compared between individuals with and those without nocturnal hypercapnia. Most striking was the absence of a relation between nocturnal hypercapnia and forced vital capacity (FVC). Some individuals had nocturnal hypercapnia despite a normal FVC, whereas others had an FVC of <40% predicted but maintained normal nocturnal tc-P_{CO_2} values (see fig 4A).

Nocturnal oxygen desaturation was seen in 15 individuals (18.3%), 5 of whom had nocturnal hypercapnia. This generally occurred in individuals with mild or moderate OSA (median O-AHI, 19.7) and little or no CSA (median CSA event, 0.3 events/h). Therefore, oxygen desaturation cannot serve as a surrogate for
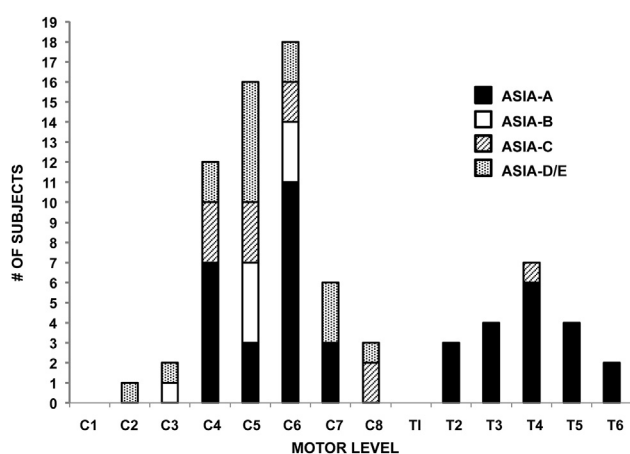
Fig 1 Distribution of SCI motor levels and motor completeness (ASIA grades).[20] Abbreviation: ASIA, American Spinal Injury Association.
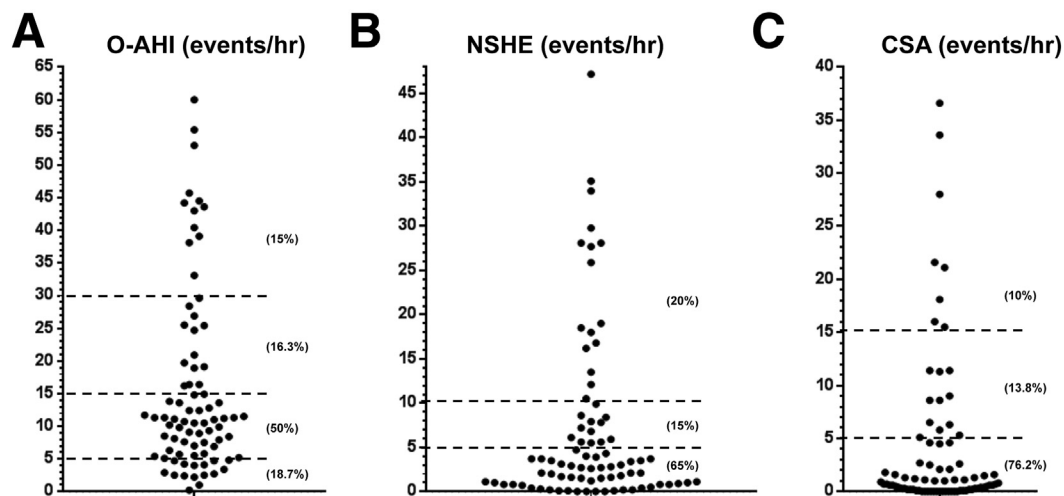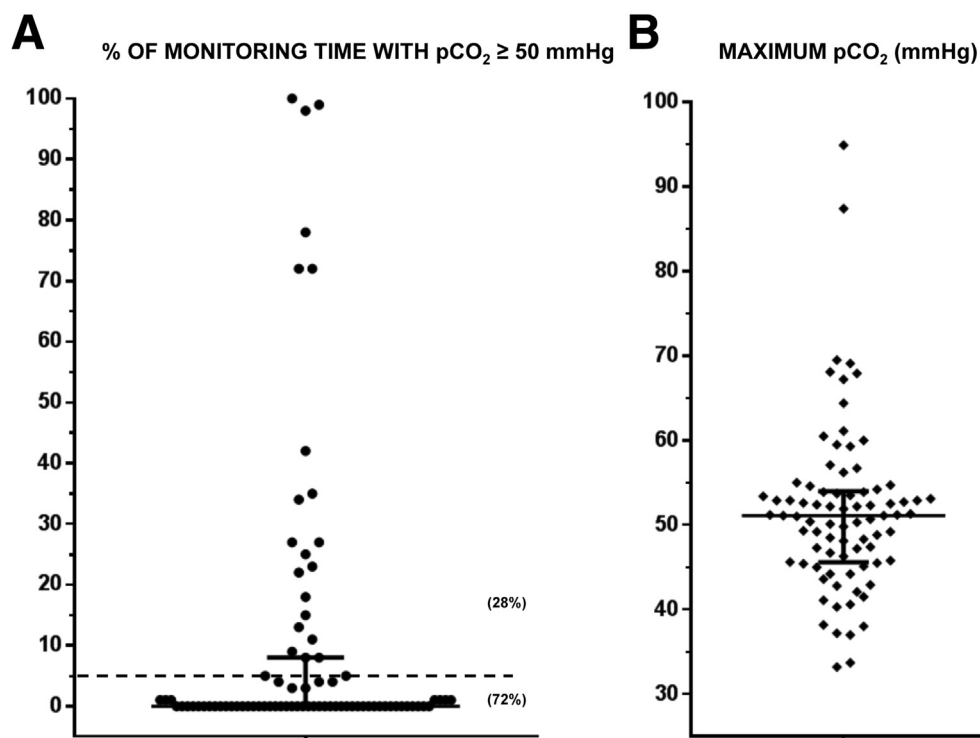
Fig 2 Scatterplots of PSG results for all study individuals, expressed as number of events per hour of monitoring time: (A) O-AHI; (B) nonspecific hypopnea events (events/h); (C) CSA events (events/h).

tc-P_{CO_2} measurement and does not necessarily reflect the severity of either OSA or CSA.

Discussion

In this study, we demonstrated the use of unsupervised home-based type III sleep apnea tests and tc-P_{CO_2}/Sp_{O_2} monitoring to assess sleep-disordered breathing and nocturnal hypercapnia in individuals with C1-T6 SCI. Repeat studies were infrequently required because of inadequate sleep time or technical errors with the HSAT or tc-P_{CO_2}/Sp_{O_2} monitor, and there were no instances where equipment was damaged. The practical advantages of this approach seem self-evident, as neither the individual nor their caregivers have to interrupt their jealously guarded care routines for facility-based studies, and sleep laboratories would not have to accommodate the special needs of a disabled individual with labor-intensive regimens of drugs and bowel/bladder/wound care. Moreover, individuals would not have to forgo sleeping in specialized wound care beds or access to specialized equipment

Fig 3 Scatterplots of tc-P_{CO_2}/Sp_{O_2} monitoring results for all study individuals: (A) duration of hypercapnia, expressed as percentage of monitoring time with $P_{CO_2} \geq 50$ mmHg; median and interquartile range are shown; (B) maximum P_{CO_2} (mmHg) detected during the monitoring period; median and interquartile range are shown.
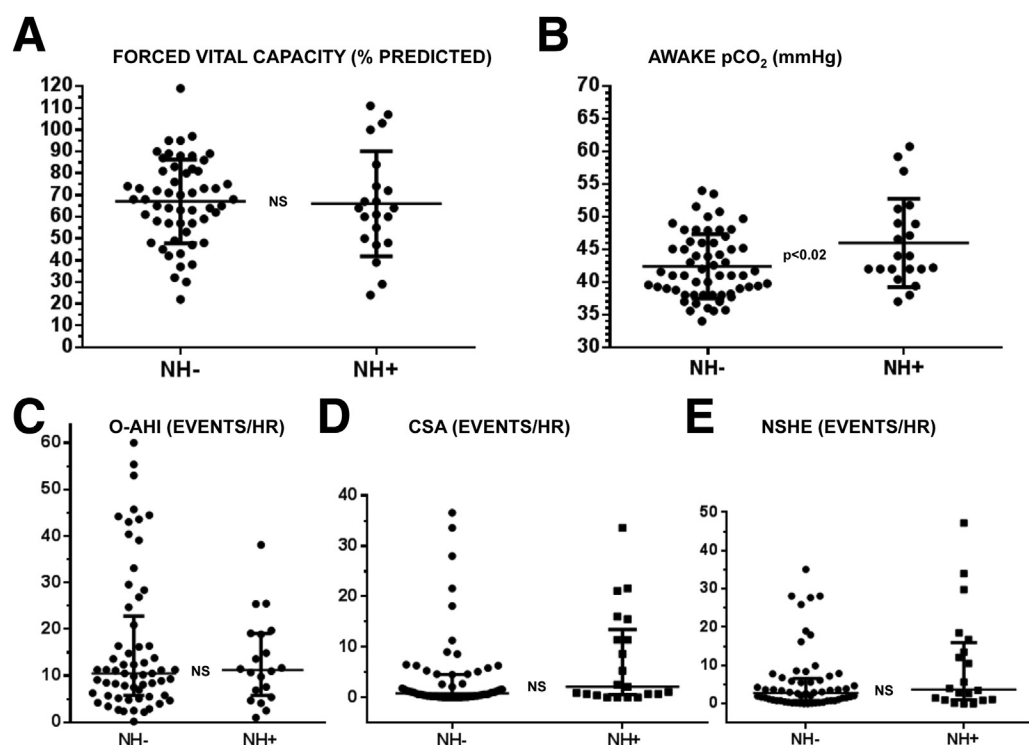
Fig 4 Scatterplots comparing individuals NH+ ($P_{CO_2} \geq 50$mmHg for $\geq 5\%$ of the monitoring time) and those NH−: (A) FVC (% predicted), with mean ± SD; (B) awake P_{CO_2} (mmHg), with mean ± SD; (C) O-AHI (events/h), with median and interquartile range; (D) CSA events (events/h), with median and interquartile range; (E) nonspecific hypopnea events (events/h), with median and interquartile range. Abbreviations: NH+, with nocturnal hypercapnia; NH−, without nocturnal hypercapnia.

for safe lifting and transfers. Avoiding these changes in the individual's routine should also alleviate concerns that the results would have been altered by disruptions in the individual's environment.

There is increasing evidence that home-based sleep apnea tests are as effective as facility-based PSG in predicting short-term responses to treatment for OSA.[24,29,30] Questions raised regarding HSATs relate to an accurate detection of OSA in low-prevalence populations,[31] but individuals with SCI have a high prevalence of OSA.[1,2,4,32-34] There are no studies in individuals with SCI that directly compare HSATs with facility-based PSG. Although such direct comparisons would be useful, they were not of practical consideration for many individuals who were eligible for this study because they had already refused to perform facility-based testing. It is reassuring, however, that despite significant differences in equipment and diagnostic criteria, these results strikingly parallel those obtained from both home-based and facility-based studies. Berlowitz et al[1] reported OSA in 60% to 83% within 2 weeks of injury, persisting on sequential PSG over 12 months. Leduc et al[2] reported OSA in 53% in outpatients with SCI assessed by full PSG in the home setting. Sankari et al[3] reported the prevalence of OSA as 79% with facility-based PSG. The concordant results across these studies strongly support the conclusion that the prevalence of OSA in individuals with SCI is high, regardless of the testing modalities or the specifics of the diagnostic criteria. There are many plausible reasons for the high prevalence of OSA, including the tendency for individuals with SCI to sleep in the supine position, the use of sedating drugs, obesity, and increasing neck circumference postinjury.[2,3,16,35,36] In the present study, neck

circumference is the only significant, albeit weak, predictor for the O-AHI. Other studies[1,2,37] concur, but other clinical variables, including body mass index, waist circumference, SCI level, and use of sedating drugs, have performed inconsistently as predictors. These discrepancies may be due to differences in study size, individual age, motor level, duration of injury, and diagnostic criteria. It may be instructive if future studies included verification of drug use as opposed to reliance on prescription history as in the present study.

The modified diagnostic criteria for OSA were chosen to address the concern that hypopnea due to respiratory muscle weakness may influence the diagnosis or severity assessment of OSA.[38] Specifically, that cessation or $\geq 50\%$ reduction of nasal airflow with preserved or increased chest wall movement could discriminate between OSA and hypoventilation from other causes. In most cases, these modified criteria actually had little impact on the diagnosis of OSA, but in 20%, ≥ 10 events/h were reclassified from obstructive events to nonspecific hypopnea events (see fig 2B). Therefore, most nonspecific hypopnea events were central events rather than misclassified OSA events, as the correlation between nonspecific hypopnea events and CSA events was extremely high (see appendix 1).

CSA was found in 23.8% of individuals (see fig 2C). CSA after SCI has been reported only in some studies, possibly because of differences in instrumentation and diagnostic criteria.[1,5] Recently, CSA was demonstrated in 63% of individuals with cervical SCI and 13% with thoracic SCI.[5] The overall prevalence agrees with the findings of the present study, although in this larger cohort the motor deficit level had no predictive value for CSA and instead baclofen use was the dominant predictor of CSA (see appendix 1).

The O-AHI was also associated with CSA, suggesting that some CSA events were responses to preceding OSA events. The underlying causes of CSA in SCI remain undefined; they are likely multifactorial and influenced by concurrent traumatic brain injury, sedatives, rebound hyperpnea after obstructive events, intermittent hypoxia, and altered chemoreflex sensitivity.[5]

There is little published data on overnight P_{CO_2} levels after SCI. Bach and Wang[39] reported transient hypercapnia in 4 of 10 individuals with SCI at baseline, and in all 10 when restudied 5 years later. The present study selected stable individuals with little or no prior exposure to ventilatory support; nonetheless, nocturnal hypercapnia was demonstrated in 28% of studies, often with substantial increase in tc-P_{CO_2} (see fig 3). One may expect that more symptomatic individuals, and those requiring prior bilevel PPV support, would be more likely to have nocturnal hypercapnia. In a retrospective analysis,[40] overnight tc-P_{CO_2} monitoring similarly demonstrates previously unsuspected nocturnal hypercapnia in individuals with various underlying neuromuscular disorders.

Perhaps most remarkable was that clinical and physiological variables performed so poorly in predicting nocturnal hypercapnia. As expected, there was an association between awake tc-P_{CO_2} and nocturnal hypercapnia, but it was too weak to be of clinical use (see appendix 2 and fig 4B). The absence of any relation between FVC and nocturnal hypercapnia was particularly notable, as conventional wisdom holds that respiratory muscle weakness influences the degree of hypoventilation during sleep and an FVC of <50% is a criterion for prescribing bilevel PPV in individuals with neuromuscular disorders.[41] There was no relation between FVC and nocturnal hypercapnia. This point is best illustrated by the individuals at both limits of the FVC range, as 5 of 21 with an FVC of >80% predicted still had nocturnal hypercapnia and conversely 12 of 17 with an FVC of <50% predicted did not have nocturnal hypercapnia. Study time with tc-$P_{CO_2} \geq 50$mmHg showed only marginal or no association with any other clinical predictors, after adjusting for CSA. These findings suggest that the degree of nocturnal hypercapnia is driven more by loss of ventilatory drive than by the severity of pulmonary restriction or by severe OSA. The most important point in this analysis is that neither the presence nor the absence of nocturnal hypercapnia can be predicted reliably by clinical variables or spirometry and that direct measurement by overnight tc-P_{CO_2} monitoring is required to establish its presence and to inform the decision to start or adjust bilevel PPV.

Study limitations

This study excluded individuals previously diagnosed with sleep-disordered breathing, resulting in an inability to assess whether there are clinical or physiological differences between individuals suspected to have sleep-disordered breathing and were willing and able to undergo facility-based PSG and those who were either asymptomatic or could not undergo facility-based testing. A possible disadvantage of HSATs is that in the absence of a trained observer, there are several unanswered questions such as actual duration of sleep, sleep position, sleep quality, and interruption of sleep for care needs. These unknown factors may have influenced the study results. Furthermore, it is always possible in an unsupervised study that some events (low or absent nasal airflow, poor respiratory effort signal) may be due to technical artifacts. Future studies will have to determine whether

technical modifications such as adding a thermistor to the nasal airflow sensor, a dual thoracoabdominal belt, or sensors for body position or lights on would add value to the data collection. Lastly, the data collected on sedating drugs in this study were through review of the medical record. Dosing, frequency, and timing of drug use were not confirmed by study individuals, which limits the ability to draw firm correlations between drug use and sleep-disordered breathing.

Conclusions

Home-based monitoring of clinically stable individuals with SCI is a simple and effective strategy for diagnosing sleep-disordered breathing and nocturnal hypercapnia. This strategy may substantially improve access to sleep studies and lead to earlier treatment for sleep-disordered breathing for individuals with SCI. Still, for many individuals, this approach will not always eliminate the need for facility-based PSG. We do not suggest that the more limited data obtained from an HSAT can match the accuracy of facility-based PSG; nonetheless, in many instances the results of a home-based study may be sufficiently abnormal to appropriately justify and inform a prescription for continuous or bilevel PPV. In high-risk individuals such as those with SCI, facility-based PSG can be reserved for cases where home-based studies are technically inadequate or negative, concordant with guidelines for performance of HSATs in the general population.[42] Even if the questions of sleep-disordered breathing and nocturnal hypercapnia are fully answered, poor sleep quality is still common in individuals with SCI, for reasons unrelated to any breathing disorder.[4,14,43]

Suppliers

a. Medical Graphics Corp.
b. Phillips Respironics.
c. SenTec AG.
d. R Core Development Team 2015.

Keywords

Hypercapnia; Rehabilitation; Spinal cord injuries

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Acknowledgments

Appendix 1 Predictors of Sleep-Disordered Breathing

log O-AHI	r	P
Age	.234	.037
Neck circumference	.412	.000
Waist circumference	.243	.037

Nonsignificant correlations with log O-AHI: SCI level, SCI duration, body mass index, FVC, baclofen level, benzodiazepine use, other sedating drug use.

log O-AHI: Ordinary least-squares regression (OLS)

Predictor	Coefficient	SE	P
Neck circmference	.0905	.032	.006
Waist circumference	−.0044	.008	.570
SCI level	.0355	.032	.286

One representative model is shown; after accounting for neck circumference in multiple OLS models, there were no significant predictors for log O-AHI.

EFFECT SIZE: The standardized coefficient predicts how many SD a dependent variable will change per SD increase in the predictor variable. The standardized coefficient for neck circumference is .375, so a 1 SD change in neck circumference would be associated with a 45% change in O-AHI after controlling for other predictors.

log CSA (events/h)	r	P
Baclofen use	.342	.003
Other sedating drug use	.302	.009
log O-AHI	.332	.002

Nonsignificant correlations with log CSA: age, SCI level, SCI duration, body mass index, FVC, neck circumference, waist circumference, benzodiazepine use.

log CSA (events/h): Ordinary least-squares regression

Predictor	Coefficient	SE	P
Baclofen use	.6231	.296	.039
log O-AHI	.3328	.132	.014
Other sedating drug use	.4118	.272	.135
Age	.0140	.164	.146

One representative model is shown; in other models, there were no significant predictors for CSA after adjusting for baclofen use.

EFFECT SIZE: The standardized coefficient (defined above) for baclofen use is .258, predicting a 29% change in CSA events per hour after controlling for other predictors.

log NSHE (events/h)	r	P
log CSA (events/h)	.866	.000
log O-AHI	.308	.002

Nonsignificant correlations with log NSHE: age, SCI level, SCI duration, FVC, neck circumference, waist circumference, baclofen use, benzodiazepine use, other sedating drug use.

log NSHE (events/h): Ordinary least-squares regression

Predictor	Coefficient	SE	P
log CSA	.8636	.061	.000
log O-AHI	.0127	.078	.871
Age	.0059	.005	.249

One representative model is shown; there were no demonstrable associations with any parameters of body shape in any of the models.

EFFECT SIZE: The standardized coefficient (defined above) for log CSA is .881, so a 1 SD change would be associated with a 2.5-fold change in log NSHE (events/h) after controlling for other predictors.

Appendix 2 Predictors of Nocturnal Hypercapnia

log % time with P_{CO_2}>50mmHg	r	P
Awake P_{CO_2}	.369	.001
Baclofen use	.267	.020
log CSA (events/h)	.250	.028
Neck circumference	−.239	.036

Nonsignificant correlations with age, SCI level, SCI duration, O-AHI, FVC, benzodiazepine use, use of other sedating drug, waist circumference.

log % time with P_{CO_2}>50mmHg: Ordinary least-squares regression

Predictor	Coefficient	SE	P
Awake P_{CO_2}	.0833	.032	.010
Baclofen use	.4625	.438	.294
log CSA (events/h)	.2862	.173	.102
Waist circumference	−.0134	.010	.190

One representative model is shown; in another regression model, waist circumference was a weak negative predictor after adjusting for CSA.

EFFECT SIZE: The standardized coefficient (defined above) for awake P_{CO_2} is .448, so a 1 SD change would be associated with a 57% change in log % time with P_{CO_2}>50mmHg after controlling for other predictors.

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DRAFT DOCUMENT: MANUSCRIPT IN SUBMISSION

Positive airway Pressure Therapy for Sleep Disordered Breathing in Individuals with Spinal Cord Injury: Adherence and Short-Term Benefits

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Abstract

Objective: To evaluate the effectiveness of and adherence with bi-level positive airway pressure (PAP) therapy for sleep disordered breathing (SDB) in individuals with spinal cord injury (SCI).
Design: Prospective, cohort study
Setting: Academic tertiary care center
Participants: 91 adults with C1-T6 SCI of ≥ 3 months duration were studied for 16 months.
Interventions: Individuals with SDB but no nocturnal hypercapnia (NH) were prescribed auto-titrating PAP. Those with NH were prescribed PAP with volume-assured pressure support.
Outcome measures: Device downloads-and overnight transcutaneous capnography were performed at 3, 6, and 12 months to evaluate PAP adherence and effectiveness. Subjects kept daily event logs, and quality of life (QOL) questionnaires and laboratory testing for glucose intolerance and dyslipidemia were performed after 3, 6, and 12 months.
Results: 45% of the initial 90 participants completed the study. After 3 months, PPV was used only 33% of days, and for185 min/night on nights used (median). PAP therapy was effective in improving OSA in 88.9% and nocturnal hypercapnia in 76.5%. Higher PAP pressures predicted adherence. There were significant reductions in symptoms of autonomic dysreflexia (AD) and orthostatic hypotension as well as improved indices of QOL, but there were no significant effects on glucose tolerance or dyslipidemia.
Conclusion: PAP has short-term benefits with regard to QOL and blood pressure stability for individuals with SCI and SDB despite low adherence to treatment.

Introduction

Obstructive sleep apnea (OSA) is very common in individuals with spinal cord injury (SCI) with studies almost uniformly finding a prevalence of 40-80%.[1-6] This prevalence is remarkably high relative to the 2-9% reported for healthy subjects.[7, 8] Other forms of sleep-disordered breathing in SCI may include central sleep apnea (CSA) and nocturnal hypoventilation (NH) with estimated prevalence of up to 60% and 28% respectively.[6,9] Level of motor deficit, neck circumference, abdominal girth, respiratory muscle weakness, reduced ventilatory drive during sleep, analgesics and other sedating medications may be contribute to sleep disordered breathing (SDB) after SCI, but they have not been shown consistently to do so.[1,3,6]

In the general population, OSA is associated with increased risk for myocardial infarction, stroke, congestive heart failure, and the "metabolic syndrome" (increased visceral fat, hypertension, glucose intolerance, and hyperlipidemia).[10-17] We know very little about the adverse clinical consequences of SDB in individuals with SCI.[18] Standard treatment of SDB is provided by non-invasive positive airway pressure (PAP) therapy. In 2009, the Centers for Medicare & Medicaid Services adopted a requirement of 4 hours of PAP use on 70% of nights, or 21 days in a consecutive 30-day period, to continue medical coverage for PAP therapy.[19] Adherence in the general population with use of these devices is typically low, with most studies demonstrating near 50% long-term compliance, with rates rarely as high as 80%.[19-21] Factors associated with low adherence are low socioeconomic status, claustrophobia, post-traumatic stress disorder, PAP side effects such as air leakage, skin abrasion, and mask discomfort; nasal congestion; dry throat; and frequent awakenings.[22-25] The mode of PAP delivery such as CPAP, auto-titrating PAP and bi-level PAP may also influence adherence.[26-28]

There are few studies addressing treatment of SDB in individuals with SCI.[18, 29] A retrospective review of subjects with SCI and sleep apnea found that only 43% were receiving PAP treatment and the majority of those not receiving treatment had been intolerant of PAP or had refused. The most common reason cited for intolerance was mask discomfort. Additionally, there was a significantly lower adherence rate in patients with high-level motor complete injuries.[18] A prospective study of auto-titrating CPAP in 14 individuals with acute SCI and OSA found an adherence rate of 50% and an improvement in sleepiness over 3 months of treatment.[29] Health-related quality of life did not seem to be greatly affected by CPAP treatment.[29] It is likely that for SCI patients, sleep is often disturbed not only by SDB, but also by other factors such as care requirements, pain, and spasticity. This raises the possibility that factors determining adherence to SDB treatment may be entirely distinct the general population. Similarly, the complex comorbidities of the SCI patient may affect the benefits of SDB treatment.

The goals of the present study were to prospectively evaluate adherence with PAP therapy in individuals with SCI and SDB using data recorded by the PAP device, rather than relying on patients' histories or survey data. Factors which might influence adherence such as mask type, device settings and level of SCI were assessed. Secondly, we examined whether treatment of SDB influences common comorbidities of SCI such as pulmonary complications, autonomic dysreflexia, pain, orthostatic hypotension, glucose intolerance, or dyslipidemia. Lastly, we sought to determine whether treatment of SDB influences quality of life indices.

Methods

Permission was provided by the University of Michigan Institutional Review Board, project HUM00051504. The study was performed between March 2012 and December 2015. Eligibility was determined by reviewing the University of Michigan SCI Model System database, which includes >90% of SCI patients in the region. Subjects were eligible if ≥18 years old, with C1-T6 spinal cord injury of ≥ 3 months duration, and lived within 100 miles of the study site. Exclusion criteria included: inability to provide informed consent, comorbid condition that limited life expectancy to ≤ 1 year, active duty military personnel, ventilator-dependence, established diagnosis of sleep-disordered breathing or prior use of noninvasive positive pressure ventilation, except during a hospitalization ≥3 months prior to enrollment.

At enrollment, subjects were provided daily event logs to record episodes with symptoms of autonomic dysfunction, respiratory infections, and episodes of mucus plugging/atelectasis to be completed for a four-month observation period, and for 1 year after initiation of the study. (Appendix 1) At the initiation of the study period (month 0), height, weight, blood pressure, waist circumference, neck circumference and body mass index (BMI) were measured, and medical records were reviewed. Participants were compensated with $50 at month 0 and every 3 months thereafter. Motor level and completeness of SCI were determined according to the International Standards for the Neurological Classification of Spinal Cord Injury.[30] At month 0, SF-12v.2, Brief Pain Inventory-SF (BPI) and Epworth Sleepiness Scale (ESS) questionnaires (Appendix 2) were administered and serum lipid profile (cholesterol, low-density lipoproteins (LDL), triglyceride, high-density lipoproteins (HDL), cholesterol/HDL ratio, fasting glucose, and hemoglobin A1C (glycosylated hemoglobin) levels were performed. A two-hour glucose tolerance test was also performed, unless the subject had an established or presumptive diagnosis of diabetes mellitus. Quality of life questionnaires, device downloads, and laboratory tests were performed at 3, 6 and 12 months. Event logs were collected every 3 months for the year of follow-up. Figure 1 details the study protocol.

At month 0, SDB was assessed in subjects' homes with a home sleep apnea test (HSAT) combined with overnight oxygen saturation (SpO_2)/transcutaneous pCO_2 (tc-pCO_2) monitoring as previously described in detail.[6] Subjects diagnosed with nocturnal hypercapnia were prescribed bi-level positive airway pressure-average volume-assured pressure support (BiPAP-AVAPS; Respironics, Murraysville PA). Initial settings were: respiratory rate 10-12, expiratory PAP (EPAP) 6 cmH_2O, inspiratory PAP (IPAP) minimum 12 cmH_2O and maximum 25 cmH_2O, target tidal volume 8 mL/kg. This device maintains the programmed EPAP and auto-titrates the IPAP to achieve the target average tidal volume; other setting adjustments were made as needed for patient comfort and effectiveness. Individuals with SDB but no hypercapnia were started on bi-level positive airway pressure-Auto (BiPAP-Auto; Respironics). Initial settings were EPAP minimum 5 cmH_2O and maximum 9 cmH_2O, IPAP minimum 8-12 cmH_2O and IPAP maximum 25 cmH_2O with further settings as needed for patient comfort and effectiveness. This device auto-titrates the EPAP to control apneic events, and the IPAP to control hypopneas. The patient/device interface was based on the patient's preference and effectiveness (acceptable level of leak). Adherence data was obtained via device download at 3, 6, and 12 months. Overnight home SpO_2/ tc-pCO_2 monitoring was repeated at 3, 6, and 12 months. Individuals without SDB were not prescribed a BiPAP device but completed symptom logs, questionnaires and blood work per protocol.

<u>Statistical Analysis:</u>

The event log data was dichotomized based upon whether 1 or more events were recorded for a given subject. The observations were paired by subject and the event rates were compared using homogeneity analysis methods based on McNemar's test. Mean quality of life questionnaire scores were compared for each follow-up interval relative to baseline. The data are paired by individual, and paired Student t-tests were used to assess for a difference in means. For adherence analysis, either the percentage of days used or the number of minutes per night on nights of use were used as dependent variables in linear regression models. Clinical variables were assessed together, regardless of device type (BiPAP-auto vs. BiPAP/AVAPS), as we showed previously that the presence or absence of nocturnal hypercapnia was not predicted by these factors.[6] Because BiPAP-AVAPS and BiPAP-auto titrate settings according to different algorithms, the predictive value of the device parameters (IPAP, EPAP, exhaled tidal volume (Vte) were examined separately with device type-specific models. All analyses were performed using R version 3.1 software.

Results

Of 252 subjects contacted, 91 eligible subjects agreed to participate. 75 male and 16 female subjects, age 47.7 ± 12.3 years (mean $\pm$ SD, range 20-75 years) enrolled. Subjects were 16.8 ± 12.0 years post-injury (mean $\pm$ SD, range 1-50 years). The distribution of SCI motor levels and American Spinal Injury Association (ASIA) classification are detailed in our previous publication.[6] Seventy-four individuals underwent HSAT and $SpO_2/tc\text{-}pCO_2$ testing; overall 81.3% had evidence of obstructive sleep apnea, 23.8% had central sleep apnea (CSA) and 28% had nocturnal hypercapnia.[6] Forty were prescribed BiPAP-auto for OSA $\pm$ CSA and 23 were prescribed BiPAP-AVAPS for SDB with hypercapnia. Only 11 individuals did not have SDB. Sixty participants agreed to initiate PAP support, 3 declined. Overall, fifty patients did not complete the entire 12 month study (2 deaths, 48 withdrawals), Figure 1.

At 3 months device downloads and $SpO_2/ tc\text{-}pCO_2$ results were analyzed. The median percent of days with PPV device use was 33, IQR 8.5-85 (Figure 3) and 39% were using PPV $\geq$ 50% of nights. While adherence improved in a few subjects and declined in a few others after month 3, overall there was no significant difference in PPV device adherence at 6 and 12 months (data not shown).

After 3 months, 27 individuals were using BiPAP-Auto for OSA $\pm$ CSA and 16 (59.3%) and had an apnea-hypopnea index (AHI) of < 5 events/hr. In the 11 (40.7%) with an AHI > 5 events/hr at 3 months, only 3 (11.1%) had an obstructive apnea index (OAI) of > 5 events/hr. Therefore, BiPAP-Auto was effective in treating OSA in 88.9% of subjects. There was residual central apnea in four (14.8%) individuals at month 3. Overall, at month 3, there were 3.2 ± 3.9 central events/hr (of the 4 with >5central events/hr and <50% of events, the mean was 11.4 events/hr; range 6.9-15.9). There was only 1 subject that required a change in device, and that occurred in the first 3 months of treatment. BiPAP-Auto did not worsen central apnea in the majority of subjects, as there were only 2 with increased central events, and under 3 events/hr.

At 3 months, 17 individuals were using BiPAP-AVAPS for NH $\pm$ OSA/CSA. The BiPAP-AVAPS software does not distinguish obstructive vs. central vs. hypopnea episodes. A majority 13 (76.5%) had improvement in the AHI, 6 (35.3%) with an AHI <5. Nocturnal hypoventilation completely resolved in 8 (47%), another 5 (29.4%) had some improvement, while 1 (5.9%) had worsening NH and 3 (17.6%) did not complete 3 month testing.

To determine whether there were predictors for PPV device adherence in individuals with SCI, we examined individual clinical variables, device type and device settings. Over the first 3 months of PPV use, the percent of days the device was used (% days used) or minutes per night (min/night) of use on days used were not predicted by the SCI level, or the severity of SBD (sum of obstructive, central, and hypopnea events).[6] Additionally, individuals prescribed BiPAP-Auto were no more or less likely to be adherent with therapy than those prescribed BiPAP-AVAPS. Mask type (nasal or nasal pillows versus nasal/oral or total face mask) also did not predict either % days used or minutes/night of PPV use.

At month 3, in individuals prescribed BiPAP-Auto, average EPAP had significant predictive value for both % days used and minutes/night (p=0.04) and % days used (p=0.039). For individuals prescribed BiPAP/AVAPS, average IPAP had significant predictive value for both mins/night used (p=0.014) and % days used (p=0.048). (Table 2)

Daily event log completion rates were 96.3% at month 0 and 84.2% at month 3. There were significant reductions in the frequency of autonomic dysreflexia symptoms, orthostatic hypotension and pulmonary symptoms at several time points, while reductions in unscheduled physician visits, respiratory infections and hospitalizations were not statistically significant. In an intention to treat analysis, respondents at 6 months reported significant reductions in the frequency of symptoms suggesting autonomic dysreflexia reactions (flushing, piloerection, nasal congestion, headache, or sweating), p = 0.013 and orthostatic hypotension (lightheadedness or dizziness when sitting up or changing position) p = 0.011 compared to month 0. (Figure 3) The frequency of days with pulmonary symptoms (requiring more than usual treatments to clear secretions, or an increase in oxygen use) decreased significantly at 12 months, p = 0.041. (Figure 3) Unfortunately, there could be no valid comparison to the 11 subjects without SDB, as they had very few of these events at baseline (month 0; 3 with dizziness, 2 with autonomic dysreflexia symptoms, and no other events).

Participants were also asked to complete the SF-12v.2, Brief Pain Inventory-SF (BPI) and Epworth Sleepiness Scale (ESS) quality of life surveys at enrollment and at 3, 6 and 12 months. (Appendix 2) In an intention-to treat analysis, the ESS decreased from a mean of 8.3 to 6.8 (p = 0.007) between month 0 and month 12. Table 1 lists the survey questions for which were statistically significant changes in responses in at least one time point during the 12 months of study. The 11 individuals without SDB were also asked to complete surveys per study protocol. In general, there were not significant changes in responses, with 2 exceptions as shown in Table 1.

At initial evaluation, 7 subjects (9.1%) had previously been diagnosed with diabetes mellitus (DM). An additional 3 met the diagnostic criteria for DM based on an elevated 2 hour post-prandial glucose level, and 1 met the diagnostic criteria for DM because of an elevated Hemoglobin A1C level. Therefore, a total of 11/75 (14.7%) had at least one criterion for established or presumptive DM. A prior diagnosis of hyperlipidemia was present in 19.7% at month 0. At month 0, there were elevated cholesterol levels in 1.3%, a low HDL level in 37.3%, an elevated LDL level in 2.7%, an elevated cholesterol/HDL ratio in 14.7%, and an elevated triglyceride level in 10.7%. Fasting glucose, hemoglobin A1C, and blood lipid panels were repeated at months 3, 6, and 12. On an intention-to-treat basis, prescribing PAP for SDB did not result in any significant improvements in of these laboratory studies relevant to the metabolic syndrome.

Discussion

In this study we evaluated bi-level PPV therapy for treatment of sleep-disordered breathing (SDB) in individuals with SCI. The risk of SDB after spinal cord injury is much higher than that of the able-bodied general population.[1-6,9] Factors such as level of motor deficit, neck circumference, abdominal girth, respiratory muscle weakness, reduced ventilatory drive during sleep, analgesics and other sedating medications may contribute to the high prevalence.[1,3,6] Given that OSA is a risk factor for motor vehicle accidents which cause a significant number of SCI in the US, selection bias is also possible.[29, 31]

We have recently shown that unsupervised, home based sleep apnea testing with transcutaneous capnography is an effective and practical approach for diagnosing SDB in individuals with SCI.[6] This study reports the treatment and follow-up of this patient cohort, the first and largest prospective study of the SDB treatment in SCI. Adherence with PAP therapy both in the general population and in individuals with SCI is low.[18-21, 29] In many cases, patients refuse to even trial PAP therapy. In this study, the majority of individuals diagnosed with SDB agreed to initiate PAP therapy. At 3 months, the median days of use was only 33%. This number did not differ significantly between months 3, 6 and 12.

This is the first study in SCI where device downloads were used to assess adherence and effectiveness of treatment, as opposed to patient history or survey information. In this study, we attempted to find if there were any factors that could predict which individuals would be more likely to be adherent with PAP use. The severity of SDB, level of SCI, mask type and device type had no significant predictive value. Our data does suggest that there are differences in adherence that are a function of device-specific settings. (Table 2) In individuals prescribed BiPAP-Auto, the average EPAP was a significant predictor of device use, as a higher EPAP resulted in increased use (both % of nights of use and minutes of use per night). Further, for individuals using a BiPAP/AVAPS device, a higher level of IPAP correlated with increased use. This was somewhat surprising as clinicians often assume that higher pressures have a negative impact on adherence. It is possible that the higher pressure settings were, in fact, more comfortable, improved sleep quality, or provided unintended feedback to the patient that the treatment was more therapeutic. The higher pressures are not surrogates for the severity of SDB, as severity indices themselves had no predictive value for adherence. Further, the auto-titrating algorithms were highly successful overall, so higher pressures did not select a subgroup with more effective treatment. In retrospect, we suspect that in future studies, % days used as a parameter of adherence may require somewhat different treatment than minutes/night on days of use. Many subjects reported that they would discontinue PPV treatment for significant periods when they had unrelated illnesses such as urinary tract infections or infected sacral ulcers. They often expressed the opinion that PPV was only tolerable when their clinical status was relatively stable. In addition, they often related that minutes/night was a function of overall sleep quality, comfort, or perceived benefit. While many important questions remain, these findings show that adherence with PPV is suboptimal and significantly less than suggested by patient-reported data. In subsequent studies, it may be necessary to collect detailed survey information on a daily basis to ascertain what determined the level of use for the previous night. Given the effectiveness of PAP therapy for SDB, future studies to inform how best to ensure adherence with use are paramount.

Individuals with SCI have unique medical comorbidities, including symptoms of autonomic dysreflexia, orthostatic hypotension, impaired cough strength and increased risk of pulmonary infections/pneumonia and pain. In this study, we evaluated whether treatment of SDB

has short-term benefits toward these medical comorbidities, symptoms, and quality of life. This is the first study to do so. SDB has been associated with increased sympathetic activity, which plausibly could impact autonomic stability, specifically clinically significant blood pressure fluctuations.[32,33] Notably, there were substantial and highly significant reductions in the frequency of autonomic dysreflexia symptoms and orthostatic hypotension at several time points. (Figure 3) In addition, there was a delayed improvement in the frequency of days with increased pulmonary symptoms, while reductions in unscheduled physician visits, respiratory infections and hospitalizations did not change significantly. This may be partly due to the relatively low frequencies of these events, compared to the symptoms of blood pressure instability, so any benefits in these areas may require a larger study. To our knowledge, this is the first evidence that SDB treatment affects BP stability in SCI patients. However, it is entirely plausible, since SDB is associated with sympathetic hyperactivity and is a risk factor for hypertension in the general populations.[32,33]

We administered three quality of life surveys. (Table 1, Appendix 2) Despite the suboptimal and variable device use from night to night, there were several areas of improvement in quality of life on an intent-to-treat basis. While there were few patients with no SDB for comparison, our data suggests that there are short-term benefits to be gained from any degree of PAP use, and this may force us to reconsider our standards for acceptable adherence to therapy. Like the event log results, it is perhaps not surprising that some of these benefits were not consistent throughout the follow-up period, given the variations in device use, the influence of common concurrent illnesses such as urinary tract or wound infections, and frequent changes in medications. Future studies comparing such symptoms between those who are highly adherent with PAP use and those who either refuse or who have low PAP adherence would also serve to strengthen our findings.

This is the first study to address whether SDB increases risks of metabolic syndrome in SCI as it does in the general population. We did not find that PAP therapy for SDB resulted in any significant improvements in laboratory indices of glucose intolerance or dyslipidemia. Possible reasons for this include low adherence and short-term follow up, but it is also important to note that dietary intake and medication changes were not controlled through the study period. While our data suggests that treating SDB does not have beneficial effects that override all these variables, a more detailed study controlling medications and other variables during a defined period of PPV adherence may produce different results. A longer-term study may also provide insight into whether cardiovascular risks associated with OSA in the general population are also seen in the SCI population.

Study Limitations

A significant limitation of this study is the high rate of subjects voluntarily leaving the study. The study started with 91 participants and at the end of 12 months only 37 were still enrolled. In most instances, we were able to use paired-data analyses, so the loss of subjects during follow-up did not skew the results indicating short-term benefits, but the progressive reduction of the number of subjects remaining in the study would be expected to have limited the power of the data analysis. Additionally, because of the high prevalence of SDB in individuals with SCI, the control group was very small. Only 11 participants had no SDB, and 4 of these left the study after Month 3. For this reason, it is difficult to attribute any possible benefits to PPV therapy, as opposed to unintended consequences of study participation or other variables. Given the very high prevalence of SDB after SCI, any future study would have to have an initial

enrollment many times larger than ours to overcome these limitations. Another limitation is the low and variable adherence with PAP therapy, a problem that plagues all studies of this type. However, data from studies such as ours may still inform future studies to target important determinants of day-to-day adherence to therapy.

Conclusion

Positive airway pressure therapy has short-term benefits with regard to quality of life and blood pressure stability for individuals with SCI and SDB despite low adherence to treatment.
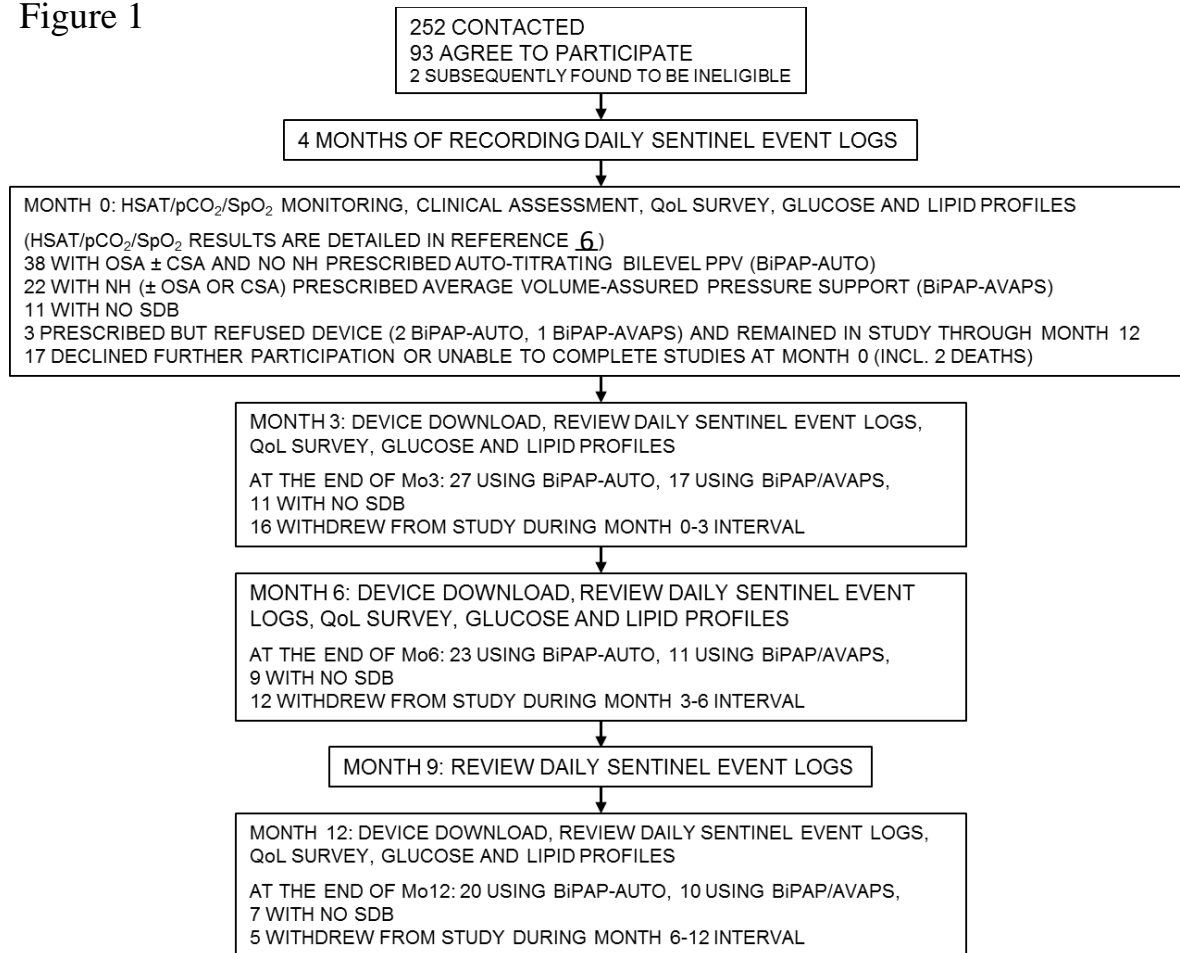
Figure 1

252 CONTACTED
93 AGREE TO PARTICIPATE
2 SUBSEQUENTLY FOUND TO BE INELIGIBLE

↓

4 MONTHS OF RECORDING DAILY SENTINEL EVENT LOGS

↓

MONTH 0: HSAT/pCO_2/SpO_2 MONITORING, CLINICAL ASSESSMENT, QoL SURVEY, GLUCOSE AND LIPID PROFILES

(HSAT/pCO_2/SpO_2 RESULTS ARE DETAILED IN REFERENCE 6)
38 WITH OSA ± CSA AND NO NH PRESCRIBED AUTO-TITRATING BILEVEL PPV (BiPAP-AUTO)
22 WITH NH (± OSA OR CSA) PRESCRIBED AVERAGE VOLUME-ASSURED PRESSURE SUPPORT (BiPAP-AVAPS)
11 WITH NO SDB
3 PRESCRIBED BUT REFUSED DEVICE (2 BiPAP-AUTO, 1 BiPAP-AVAPS) AND REMAINED IN STUDY THROUGH MONTH 12
17 DECLINED FURTHER PARTICIPATION OR UNABLE TO COMPLETE STUDIES AT MONTH 0 (INCL. 2 DEATHS)

↓

MONTH 3: DEVICE DOWNLOAD, REVIEW DAILY SENTINEL EVENT LOGS, QoL SURVEY, GLUCOSE AND LIPID PROFILES

AT THE END OF Mo3: 27 USING BiPAP-AUTO, 17 USING BiPAP/AVAPS, 11 WITH NO SDB
16 WITHDREW FROM STUDY DURING MONTH 0-3 INTERVAL

↓

MONTH 6: DEVICE DOWNLOAD, REVIEW DAILY SENTINEL EVENT LOGS, QoL SURVEY, GLUCOSE AND LIPID PROFILES

AT THE END OF Mo6: 23 USING BiPAP-AUTO, 11 USING BiPAP/AVAPS, 9 WITH NO SDB
12 WITHDREW FROM STUDY DURING MONTH 3-6 INTERVAL

↓

MONTH 9: REVIEW DAILY SENTINEL EVENT LOGS

↓

MONTH 12: DEVICE DOWNLOAD, REVIEW DAILY SENTINEL EVENT LOGS, QoL SURVEY, GLUCOSE AND LIPID PROFILES

AT THE END OF Mo12: 20 USING BiPAP-AUTO, 10 USING BiPAP/AVAPS, 7 WITH NO SDB
5 WITHDREW FROM STUDY DURING MONTH 6-12 INTERVAL

Figure 2. Adherence with Positive Airway Pressure Device Therapy
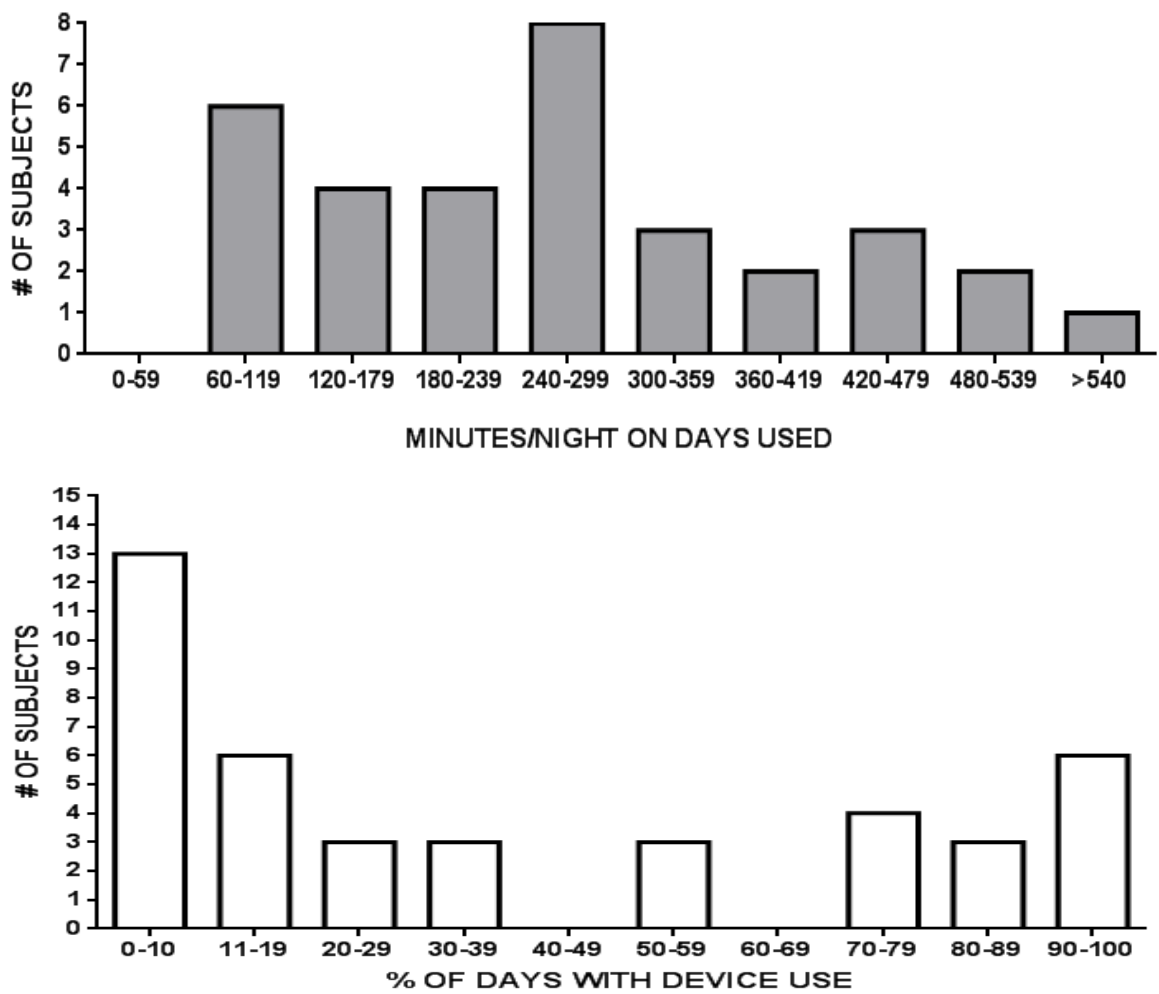
Figure 3. Daily Event Log Summary Data

A. EPISODES WITH SYMPTOMS OF AUTONOMIC DYSREFLEXIA (FLUSHING, GOOSEBUMPS, NASAL CONGESTION, HEADACHE, SWEATING)
B. ORTHOSTATIC DIZZINESS
C. DAYS REQUIRING MORE THAN USUAL TREATMENTS TO CLEAR SECRETIONS FROM LUNGS, OR INCREASE IN SUPPLEMENTAL OXYGEN
D. UNSCHEDULED PHYSICIAN VISIT FOR A LUNG PROBLEM
E. STARTED ON ANTIBIOTIC FOR LUNG INFECTION
F. HOSPITALIZATION

ALL STATISTICAL COMPARISONS ARE TO MONTH INTERVAL -4-0 (SEE METHODS). $*\ p < 0.02$; $**\ p < 0.05$

Table 1. Quality of Life Survey Responses

ALL RESPONDANTS[1]				
	Month 0	**Month 3**	**Month 6**	**Month 12**
1: In general, would you say your health is: 1: poor 2: fair 3 good 4: very good 5 excellent				
	3.3	NS	NS	3.6 (p=0.048)
3: During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health? A: Accomplished less than you would like 1: all of the time 2: most of the time, 3: some of the time 4: a little of the time 5: none of the time				
	2.9	NS	NS	3.5 (p=0.01)
5: During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)? 1. not at all 2. a little bit 3: moderately 4: quite a bit 5 extremely				
	2.8	2.4 (p=0.004)	2.4 (p=0.004)	NS
6: These questions are about how you feel and how things have been with you during the past 4 weeks. C. Have you felt downhearted and depressed? 1: all the time 2: most of the time 3: some of the time 4: a little of the time 5: none of the time				
	3.8	NS	NS	4.0 (p=0.03)
Epworth Sleepiness Scale (total points)				
	8.3	NS	NS	6.8 (p=0.007)
SUBJECTS WITHOUT SLEEP-DISORDERED BREATHING1				
13: On a scale from 0 to 10, with 0 being no pain and 10 being pain as bad as you can imagine, please rank how much pain you have right now.				
	3.9	3.0 (p=0.045)		
Epworth Sleepiness Scale (total points)				
	9.4	5.9 (p=0.007)	NS	NS

[1]ONLY QUESTIONS WITH SIGNIFICANT CHANGES FROM MONTH 0 AT ≥ TIME POINT ARE LISTED

Table 2

PREDICTOR VARIABLES OF ADHERENCE TO PPV DEVICE USE AT MONTH 3

% DAYS OF DEVICE USE

Device	Predictor Variable	Coefficient[1]	Standard Error	p
BiPAP-auto	average EPAP	10.01	4.59	**0.039**
	average IPAP	-2.78	4.06	0.5

BiPAP/AVAPS	Predictor Variable	Coefficient	Standard Error	p
	average EPAP	12.23	5.871	0.059
	average IPAP	4.67	2.12	**0.048**
	average Vte	0.052	0.034	0.159

MINUTES OF USE/NIGHT

Device	Predictor Variable	Coefficient	Standard Error	p
BiPAP-auto	average EPAP	42.12	19.43	**0.04**
	average IPAP	-2.68	17.18	0.88

BiPAP/AVAPS	Predictor Variable	Coefficient	Standard Error	p
	average EPAP	12.23	5.87	0.059
	average IPAP	4.67	2.12	**0.048**
	average Vte	0.052	0.034	0.159

1. The coefficient refers the unit change in the dependent variable for every unit change in the independent variable, based on the prediction model.

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UNIVERSITY OF MICHIGAN
SPINAL CORD INJURY
RESEARCH PROJECT

NAME _____   WEEK OF _____

SUNDAY	LUNG ◯	MD ◯	DRUG ◯	GOOSEBUMP ◯	DIZZY ◯	BP ◯
MONDAY	LUNG ◯	MD ◯	DRUG ◯	GOOSEBUMP ◯	DIZZY ◯	BP ◯
TUESDAY	LUNG ◯	MD ◯	DRUG ◯	GOOSEBUMP ◯	DIZZY ◯	BP ◯
WEDNESDAY	LUNG ◯	MD ◯	DRUG ◯	GOOSEBUMP ◯	DIZZY ◯	BP ◯
THURSDAY	LUNG ◯	MD ◯	DRUG ◯	GOOSEBUMP ◯	DIZZY ◯	BP ◯
FRIDAY	LUNG ◯	MD ◯	DRUG ◯	GOOSEBUMP ◯	DIZZY ◯	BP ◯
SATURDAY	LUNG ◯	MD ◯	DRUG ◯	GOOSEBUMP ◯	DIZZY ◯	BP ◯

MARK THE DAY(S) WHEN THE FOLLOWING SYMPTOMS OR EVENTS OCCURRED:

LUNG: You required more than your usual treatments to clear secretions from your lungs, or you had to increase your oxygen

MD: You had an unscheduled physician visit for a problem with your lungs

DRUG: You were started on an antibiotic for any infection in your lungs

GOOSEBUMP: You had episodes with symptoms including flushing, goosebumps, nasal congestion, headache, or sweating

DIZZY: You had lightheadedness or dizziness when sitting up or changing position

BP: Your blood pressure was checked and found to be over 140 or less than 80 systolic

Name_____   Date _____

SF-12v.2 HEALTH SURVEY

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

---

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
○	○	○	○	○

---

2. **The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?**

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○	○	○
b. **Climbing <u>several</u> flights of stairs**	○	○	○

---

3. **During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. <u>Accomplished less</u> than you would like	○	○	○	○	○
b. **Were limited in the <u>kind</u> of work or other activities.**	○	○	○	○	○

---

4. **During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. <u>Accomplished less</u> than you would like	○	○	○	○	○
b. **Did work or activities <u>less carefully than usual</u>**	○	○	○	○	○

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
○	○	○	○	○

6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Have you felt calm and peaceful?	○	○	○	○	○
b. Did you have a lot of energy?	○	○	○	○	○
c. Have you felt downhearted and depressed?	○	○	○	○	○

7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
○	○	○	○	○

SUPPLEMENTAL QUESTIONS

8. How many hours per week do you spend working at job for which you paid? _____

9. How many hours per week do you spend in homemaking activities, including parenting, meal preparation, and home maintenance? _____

10. How many hours per week do you spend in school, including both hours of class and time spent studying? _____

11. How many hours per week do you spend in recreational activities such as sports, exercising, going to movies, or playing games – do not include watching TV? _____

12. Do you live with a spouse or significant other? ☐ Yes ☐ No *(check one)*

QUESTIONS FROM THE BRIEF PAIN INVENTORY

13) On a scale from 0 to 10, with 0 being No Pain and 10 being Pain as Bad as You Can Imagine, please rank how much pain you have right now _____

14) On a scale from 0 to 10, with 0 being Pain Does Not Interfere and 10 being Pain Completely Interferes, how much has your pain interfered with your General Activities during the past 24 hours? _____

EPWORTH SLEEPINESS SCALE

How likely are you to doze off or fall asleep in the situations described below,
in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently, try to work out how they would have affected you.

Use the following scale to choose the <u>most appropriate number</u> for each situation.

> 0 = would <u>never</u> doze
> 1 = <u>Slight</u> chance of dozing
> 2 = <u>Moderate</u> chance of dozing
> 3 = <u>High</u> chance of dozing

Situation	Chance of dozing
Sitting and reading.	
Watching TV	
Sitting, inactive in a public place (e.g. a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in the traffic	
TOTAL	